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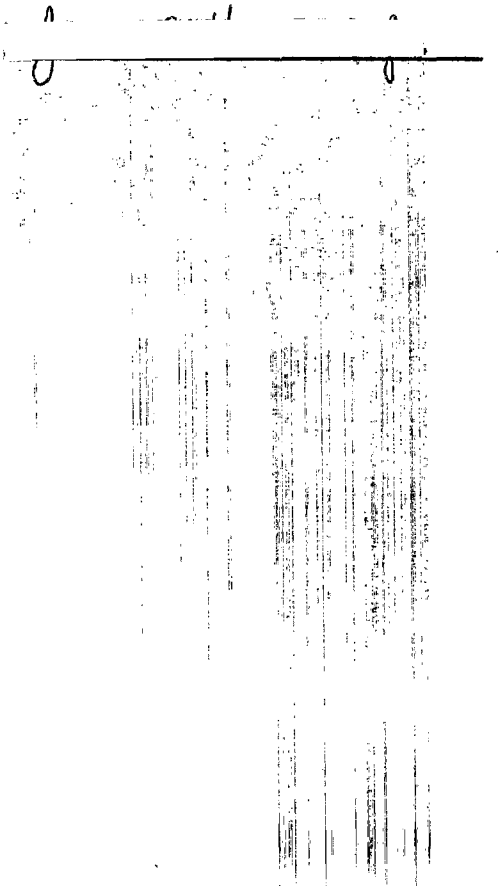


A CONTRIBUTION TO THE CHEMISTRY OF THE ANTIBIOTIC NOCARDAMINE

A THESIS

Presented to

The Faculty of the Graduate Division

by

James Alexander Hammond, Jr.

In Partial Fulfillment

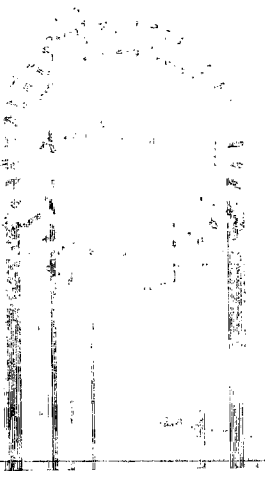
of the Requirements for the Degree

Doctor of Philosophy

in the School of Chemistry

Georgia Institute of Technology

March, 1963



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A CONTRIBUTION TO THE CHEMISTRY OF THE ANTIBIOTIC NOCARDAMINE

Approved:

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Date approved by Chairman: May 10, 1963

ACKNOWLEDGMENTS

The author is indebted to Dr. John R. Dyer for his invaluable guidance and supervision during the entire course of this research. He is grateful to Dr. R. D. Kimbrough, Jr. and Dr. J. R. Cox, Jr. for their readings of the thesis. The financial assistance afforded by a fellowship under the National Defense Education Act and by a research assistantship sponsored by the National Institutes of Health is greatly appreciated. The author would like to express special appreciation to his wife for her understanding and encouragement throughout the entire period of study.

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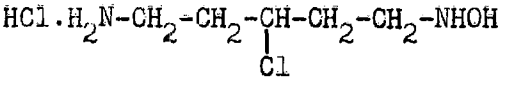
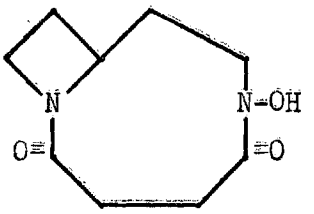
SUMMARY

The purpose of this research was to establish the correct structure of the antibiotic nocardamine. Nocardamine had previously been isolated from a species of Nocardia by other workers; the antibiotic was reported to be a crystalline, optically inactive compound of the formula $C_9H_{14}N_2O_3$. Hydrolysis of nocardamine by dilute hydrochloric acid was reported to yield succinic acid and 1-amino-3-chloro-5-hydroxylaminopentane monohydrochloride, I. It had been concluded that I was



I

produced by the cleavage of an azetidine ring in nocardamine, and that the structure of the antibiotic was II.



II

The assignment of structure II to nocardamine seemed insecure because the proof of structure for the basic compound I was not, for several reasons, rigorous.

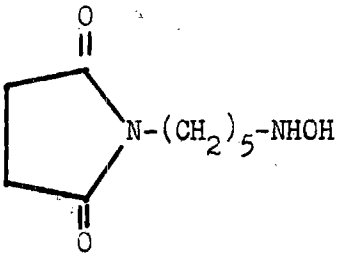
A subsequent report in the literature of the isolation (from a

natural source) and characterization of the compound 1-amino-5-hydroxylaminopentane, III, made it appear that III, rather than I, was the basic

$$HCl.H_2N\text{-}(CH_2)_5\text{-}NHOH.HCl$$

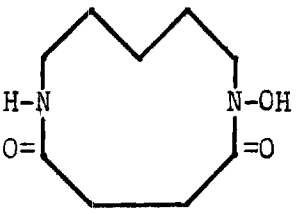
III

compound obtained on hydrochloric acid hydrolysis of nocardamine. The chemical and physical properties, including the melting point, of III are the same as those which had been reported for the hydrolysis product of nocardamine. This led to the conclusion that nocardamine possessed either the structure 1-succinimido-5-hydroxylaminopentane, IV,



IV

or the structure 1-hydroxy-1,6-diaza-2,5-dioxocycloundecane, V.

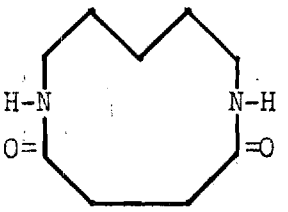


V

A synthesis of 1-succinimido-5-hydroxylaminopentane (IV) was accomplished. 1-Succinimido-5-bromopentane was prepared by the reaction of

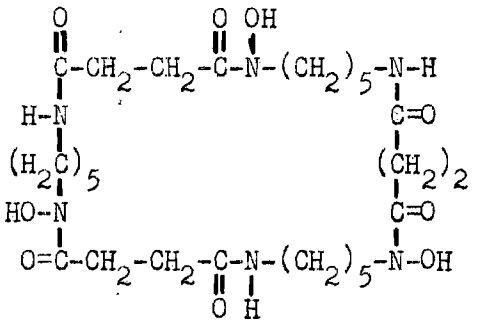
sodium succinimide with excess 1,5-dibromopentane; the reaction of 1-succinimido-5-bromopentane with hydroxylamine gave IV. The compound (IV) was found not to be identical to nocardamine.

A subsequent report by other workers suggested the structure V for nocardamine; the proof of structure included the report that the molecular weight of nocardamine was 200 - a value consistent with structure V. This assignment of structure was supported by an independent communication in which it reportedly was found that the product of hydrogenation of nocardamine was 1,6-diaza-2,5-dioxocycloundecane, VI. However, a later



VI

report in the literature rejected the structure V and suggested the trimeric structure 1,12,23-trihydroxy-1,7,12,18,23,29-hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane, VII, for nocardamine. This paper reported

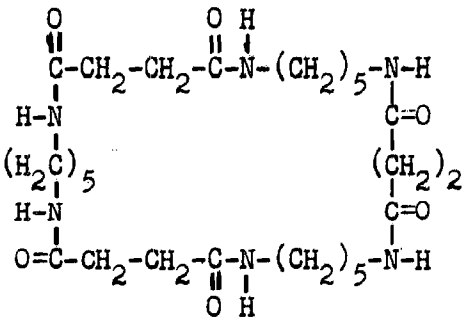


VII

that the molecular weight of nocardamine was 600 - a value consistent with

structure VII.

A resolution of this problem by means of a determination of the identity or non-identity of the reduction product of authentic nocardamine with synthetic samples of 1,6-diaza-2,5-dioxocycloundecane, VI, and 1,7,12,18,23,29-hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane, VIII, was undertaken.



VIII

A sample of authentic nocardamine was hydrogenated; the purified product, IX, melted at 279-281°. The analytical data were consistent with the empirical formula $C_9H_{16}N_2O_2$ for IX, and the infrared and nuclear magnetic resonance spectra of the compound were consistent with either of the structures VI or VIII.

1,6-Diaza-2,5-dioxocycloundecane (VI) was prepared by the reaction of succinyl chloride with 1,5-pentanediamine. The analytical data were consistent with the formula $C_9H_{16}N_2O_2$ for VI, and the molecular weight of the compound was 178 ± 16 (calc'd. for $C_9H_{16}N_2O_2$, 184). A comparison of the physical properties of VI and the reduction product of nocardamine (IX) showed that the two compounds were not identical. The melting point of VI was 218-221°; IX melted at 279-281°. VI sublimed when heated at atmospheric pressure, but IX did not sublime. The

infrared spectrum of VI was markedly different from that of IX in the region 7.50 to 14.00 μ. There was a significant difference in the solubility in water of VI and IX. The nuclear magnetic resonance spectra of VI and IX were, as expected, very similar.

A synthesis of 1,7,12,18,23,29-hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane (VIII) was attempted. 4-Oxo-5-aza-10-aminodecanoic acid (X) was prepared by the reaction of succinic anhydride with excess 1,5-pentanediamine; X was converted by reaction with carbobenzoxy chloride into 4-oxo-5-aza-10-carbobenzoxyaminodecanoic acid (XI). The reaction of XI and 1-amino-5-nitropentane with dicyclohexylcarbodiimide gave 1-carbobenzoxyamino-6,11-diaza-7,10-dioxo-16-nitrohexadecane (XII). Simultaneous reduction of the nitro group and hydrogenolysis of the carbobenzoxy group of XII by means of hydrogenation over palladium catalyst yielded 1,15-diamino-6,11-diaza-7,10-dioxohexadecane (XIII). 4,12-Dioxo-5,11-diazapentadecanedioic acid (XIV) was prepared by the reaction of 1,5-pentanediamine with excess succinic anhydride. XIII and XIV were allowed to react with two molar equivalents of dicyclohexylcarbodiimide; no material which showed the properties expected of VIII, however, could be detected in the reaction mixture.

INTRODUCTION

The antibiotic nocardamine was first described in 1951 by Stoll, Brack, and Renz (1). The compound, which showed specific bacteriostatic activity toward Mycobacterium tuberculosis, was produced by a species of Nocardia isolated from old bee honeycombs. Nocardamine was extracted from the culture broth with n-butyl alcohol, and after recrystallization from hot water, the pure, neutral compound had a melting point of 184°. It gave a red-brown color with ferric chloride solution, a silver mirror with Tollen's reagent, and reduced Fehling's solution on warming.

A subsequent paper (2) by the same workers suggested, on the basis of the analysis and the results of acid hydrolysis, the formula $C_9H_{14}N_2O_3$ for nocardamine. No molecular weight determination on the compound was reported. As obtained, the pure material was optically inactive. It gave a monoacetyl derivative which, since nocardamine showed no basic properties, was formulated as an ester rather than an amide. Hydrolysis of nocardamine by dilute hydrochloric acid produced succinic acid and a basic compound, isolated as the crystalline hydrochloride $C_5H_{14}Cl_2N_2O$ which was assigned the structure I. This basic fragment reduced ammoniacal silver solution and Fehling's solution, but gave no color with ferric chloride

$$HCl.H_2N\text{-}CH_2\text{-}CH_2\text{-}\underset{\displaystyle Cl}{\underset{|}{CH}}\text{-}CH_2\text{-}CH_2\text{-}NHOH$$

I

solution. It was reported that I had only one basic group (present as the

hydrochloride) on the basis of the titration behavior of the compound. When titrated with sodium hydroxide solution, one equivalent of alkali was absorbed to yield a free base of the formula $C_5H_{13}ClN_2O$, which was assigned structure II. The chlorine atom remaining in II was not detect-

$$H_2N\text{-}CH_2\text{-}CH_2\text{-}\underset{\displaystyle Cl}{\underset{|}{CH}}\text{-}CH_2\text{-}CH_2\text{-}NHOH$$

II

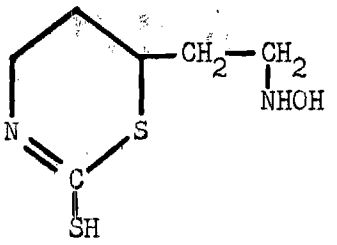
ed titrimetrically with sodium hydroxide solution; thus it was concluded that this chlorine atom was directly bonded to carbon. It was stated that on long standing in alkaline solution, this remaining chlorine atom was also removed. By acetylation with acetic anhydride and pyridine, I gave rise to a crystalline triacetyl derivative IV, $C_{11}H_{18}N_2O_4$, for which no structural assignment was made. I was regenerated from IV by hydrolysis with dilute hydrochloric acid. On reduction with tin and hydrochloric acid, I gave crystalline cadaverine dihydrochloride, III, which was identified

$$HCl.H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2.HCl$$

III

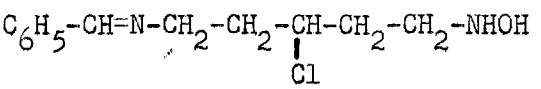
by a mixed melting point determination with an authentic sample. That one of the nitrogen-containing groups in I was a hydroxylamino group was indicated by the analytical data, by the formation of an ester on acetylation, and by the production of the diamine III on reduction. The absence of the expected basic character of this hydroxylamino group in I was attributed to the formation of an intramolecular hydrogen bond between the hydroxylamino nitrogen and the gamma chlorine atom.

Evidence presented for the presence and the positioning of the organically-bound chlorine atom in I consisted of the formation of derivatives of I with carbon disulfide and with salicylaldehyde. When I was treated with carbon disulfide in alkaline solution, there was obtained a crystalline product, the analysis of which indicated the formula $C_6H_{12}N_2OS_2$. This compound was assigned the dihydro-1,3-thiazine structure V on the basis of the analytical data and the known ring formation of γ-haloamines with



V

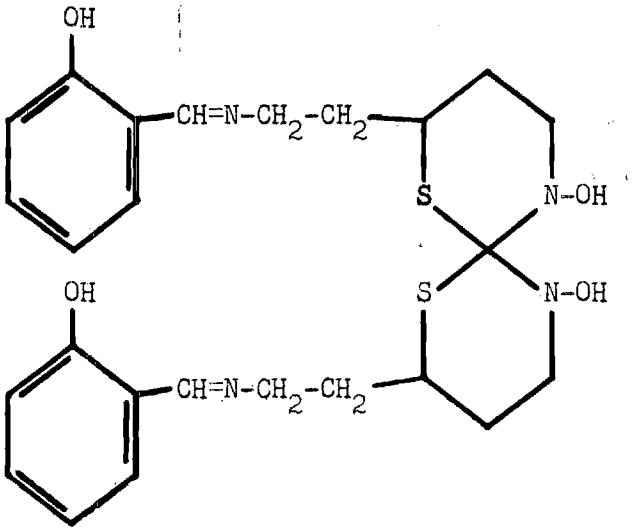
carbon disulfide (3,4,5). Reaction of I with one mole of salicylaldehyde in basic solution resulted in the isolation of a crystalline condensation product of the formula $C_{12}H_{17}ClN_2O_2$. This compound was assigned the structure VI on the basis of the analytical data. Subsequent reaction of VI with carbon disulfide in the presence of alkali yielded a crystal-



VI

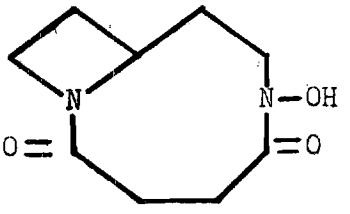
line derivative which, on the basis of the analysis and a determination of molecular weight, was tentatively assigned the structure VII. The ease of formation of these derivatives indicated that the chlorine atom in I was in a position gamma to both nitrogen functions, therefore

allowing the production of the six-membered ring in both V and VII.



VII

It was thus determined that the products of acid hydrolysis of nocardamine were succinic acid and the basic hydrochloride I. Further, it was concluded that I must have been produced by the cleavage of an azetidine ring in nocardamine, thus explaining the introduction of the organically-bound chlorine atom in I. On the basis of these data, nocardamine was assigned the structure VIII.



VIII

The work reported in this thesis was begun when the above work of Stoll and coworkers was the total accumulated knowledge of the chemistry

of nocardamine. Possible criticism of the suggested structure (VIII) for nocardamine included the following:

(1) That the hydroxylamino group in I showed no basic character due to the formation of an intramolecular hydrogen bond with the gamma chlorine atom was not convincing.

(2) It was difficult to rationalize the acetylation of the base I to the crystalline derivative IV, which contained no chlorine, and subsequent regeneration of I by hydrolysis of IV with hydrochloric acid.

(3) On reduction of the base I with tin and hydrochloric acid to yield cadaverine, the carbon-bound chlorine atom was lost. The conditions employed for the reduction were mild, and the yield of cadaverine was excellent. It is surprising that the aliphatic chlorine atom was removed so readily.

(4) The proposed structure for nocardamine contained an asymmetric carbon atom, yet the antibiotic is optically inactive. It was suggested (2) that nocardamine occurred in nature as a racemic mixture. However, instances in which natural products containing asymmetric carbon atoms have been obtained in optically inactive form are rare.

Contributions to the knowledge of the chemistry of nocardamine which have appeared in the literature during the progress of the present work have considerably clarified the structural problem. In the first of a series of papers (6) emanating from the laboratories of Dr. V. Prelog, it was shown that the base hydrochloride, previously assigned the structure I, obtained an acid hydrolysis of nocardamine was identical to the dihydrochloride of 1-amino-5-hydroxylaminopentane (IX). This latter compound had been isolated by Prelog and coworkers as an essential **hydrolysis**

product of a series of iron-containing hormones, named the ferrioxamines,

$$HCl.H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NHOH.HCl$$

IX

obtained from a culture of Streptomyces pilosus. The structure of IX was verified by synthesis. Thus the basic hydrolysis product from nocardamine contained two more hydrogen atoms than previously assumed. It was suggested (6) that the "free base", reportedly obtained on titration of the base hydrochloride with sodium hydroxide solution and assigned the structure II (2), was probably the monohydrochloride of 1-amino-5-hydroxylaminopentane, X, in which the amino nitrogen atom was protonated. The previously described acetyl derivative (IV) yielded analytical data con-

$$HCl.H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NHOH$$

X

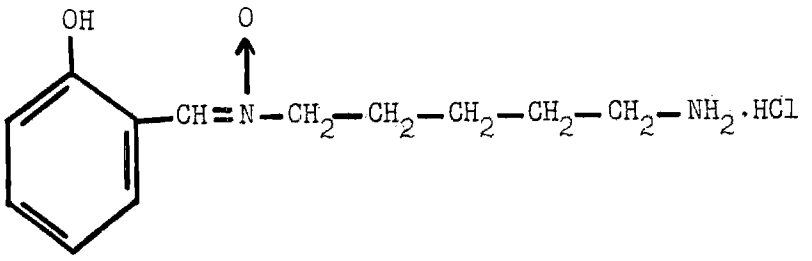
sistent with the formula $C_{11}H_{20}N_2O_4$ and was thought to be O,N,N'-triacetyl-1-amino-5-hydroxylaminopentane. The reaction product of IX with carbon disulfide, formulated earlier (2) as the dihydrothiazine derivative V, was assigned the zwitterionic dithiocarbamate structure XI on the basis of the analytical data and infrared and ultraviolet spectroscopy studies.

$$H_3\overset{+}{N}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}N(OH)\text{-}\overset{-}{C}S_2$$

XI

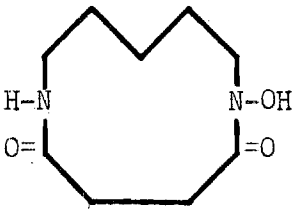
The compound formed on reaction of IX with salicylaldehyde, previously thought to be the Schiff base VI, was formulated as the hydrochloride

salt of the aldimine-N-oxide XII as the result of a study of its infrared and ultraviolet spectra.



XII

On the basis of the determination that the basic hydrolysis product from nocardamine was IX, in conjunction with the neutral character of the antibiotic, the formula $C_9H_{16}N_2O_3$ and the structure XIII were suggested for nocardamine (6). This structure was supported by infrared studies

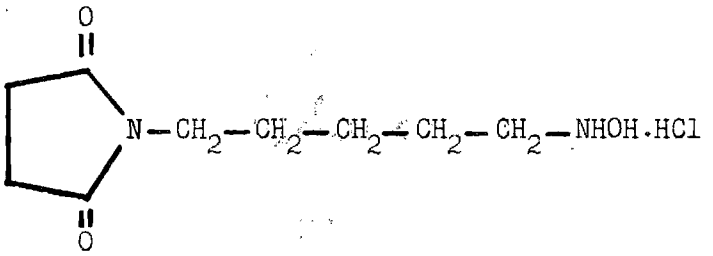


XIII

and is in agreement with the fact that nocardamine is optically inactive. A polymeric formula was excluded on the basis of experimental molecular weights of 196, 198, and 202 (calculated for XIII, 200) by the Rast method in camphor, the ebullioscopic method in pyridine, and the method of isothermal distillation in methyl alcohol, respectively (6).

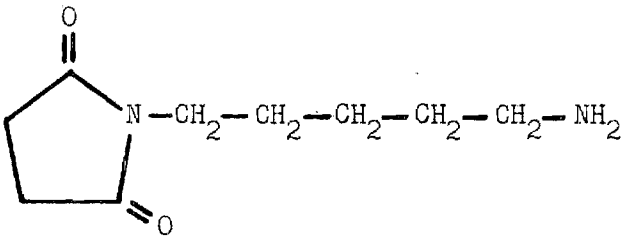
In a subsequent paper (8) concerned with the constitution of the hormone ferrioxamine B, there was reported the isolation, as a minor

product of hydrochloric acid hydrolysis of ferrioxamine B or of nocardamine, of the hydrochloride of a basic compound assigned the structure 1-succinimido-5-hydroxylaminopentane hydrochloride, XIV.



XIV

Compound XIV was obtained as an oil which gave only one spot on paper chromatography, displayed infrared absorption typical of succinimido compounds, reduced 2,3,5-triphenyl-2H-tetrazolium chloride reagent, and absorbed one mole of hydrogen to yield a liquid amine which was thought to be 1-succinimido-5-aminopentane, XV, on the basis of its analytical

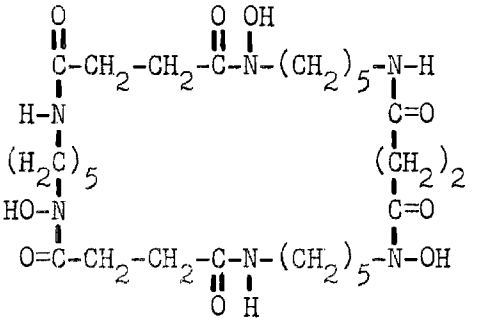


XV

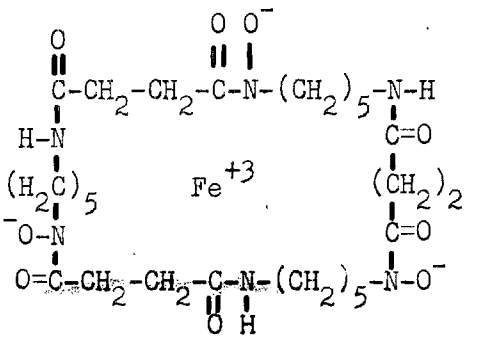
data and infrared spectrum. A later report (9) verified this assignment of structure by synthesis of the crystalline N-benzoyl derivative of XV, i.e., 1-succinimido-5-benzoylaminopentane.

The next communication (10) from this group of workers showed that the compound ferrioxamine E, which was a neutral, trihydroxamatoiron

(III) complex of the formula $C_{27}H_{45}FeN_6O_9$, yielded nocardamine on removal of the iron with aqueous sodium hydroxide solution. Ferrioxamine E could be regenerated by treatment of nocardamine with ferric chloride and sodium acetate in methyl alcohol solution. The consideration that ferrioxamine E was an iron (III) complex with three nocardamine anions (assuming nocardamine possessed structure XIII) was discarded when a re-examination of the earlier determinations of the molecular weight of nocardamine (6) showed them to be unreliable. A new determination of the molecular weight of nocardamine employing a Vapor Pressure Osmometer (11) indicated a value of 545. On the basis of these data, structure XIII for nocardamine was replaced by the trimeric 33-membered ring analog XVI (calculated molecular weight, 601), and ferrioxamine E was assigned the structure XVII.

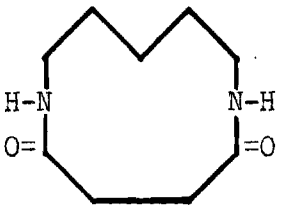


XVI

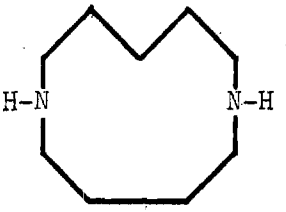


XVII

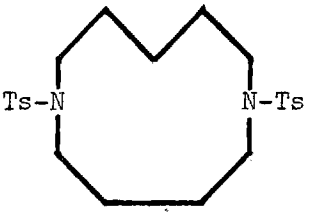
Chronologically (at least from our point of view), the next development in the nocardamine problem was a report (12) that nocardamine yielded 1,6-diaza-2,5-dioxocycloundecane, XVIII, m.p. 273°, when reduced with hydrogen and Raney nickel. This structural assignment, which was based on satisfactory analytical and infrared data, was reportedly verified by synthesis; the reaction of cadaverine with succinyl chloride in benzene solution by the high dilution method of Stetter (13) gave XVIII.



XVIII



XIX



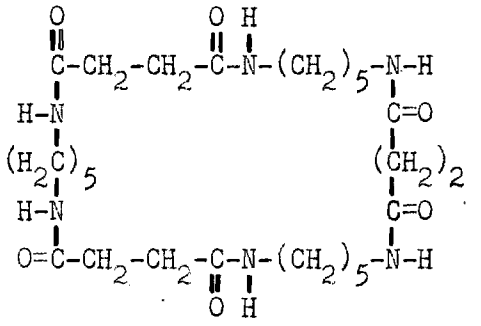
XX

On reduction with lithium aluminum hydride, XVIII was reported to yield 1,6-diazacycloundecane, XIX. XIX was synthesized by the reaction of N,N'-di-p-tosylcadaverine with 1,4-dibromobutane to yield N, N'-di-p-tosyl-1,6-diazacycloundecane, XX, followed by reduction of XX to XIX with sodium in n-butyl alcohol. The assignment of structure to compound XX was made on the basis of correct analytical data and an experimental molecular weight of 461 (calculated for XX, 465).

The course of the research reported in this thesis has necessarily been influenced by the concurrent contributions of other workers. This research was designed to verify or to determine the structure of the antibiotic nocardamine. Our approach to the problem had included, as an initial objective, a synthesis of the structure I for comparison with the basic compound obtained on hydrolysis of nocardamine. However, before

such a synthesis had been accomplished, there appeared in the literature (7) the first report of isolation and characterization of the compound 1-amino-5-hydroxylaminopentane dihydrochloride (IX). It then appeared certain that IX, rather than I, was the hydrolysis product from nocardamine. This led to the conclusion that nocardamine possessed either the structure XIII or the structure 1-succinimido-5-hydroxylaminopentane (the free base corresponding to structure XIV). An initial aim was a synthesis of XIII and XIV-base to ascertain their identity or non-identity with nocardamine.

The subsequent conflicting reports concerning the molecular weight of nocardamine (6,10,12) made a choice between structure XIII and structure XVI uncertain. The synthesis of the cyclic amides XVIII and XXI was undertaken in order to resolve this problem.

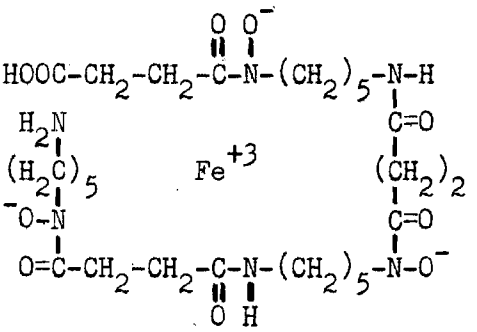


XXI

If one of these synthetic materials was truly identical with the reduction product of nocardamine, it was felt that the ring size of nocardamine would be established with certainty.

At a time when the above work was near completion, there was reported by Prelog and Walser (14) a somewhat indirect synthesis of

nocardamine. A synthesis of the hormone ferrioxamine G, XXII, was completed (14). Ferrioxamine G had previously (15) been converted by reaction

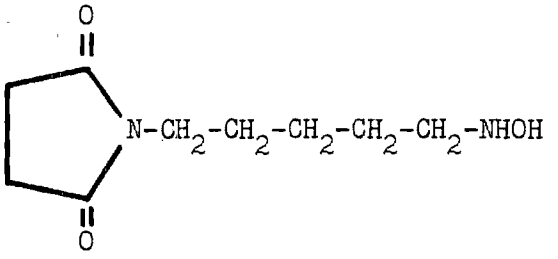


XXII

with dicyclohexylcarbodiimide into ferrioxamine E, XVII, in four per cent yield. As mentioned earlier, ferrioxamine E could be converted into nocardamine (10).

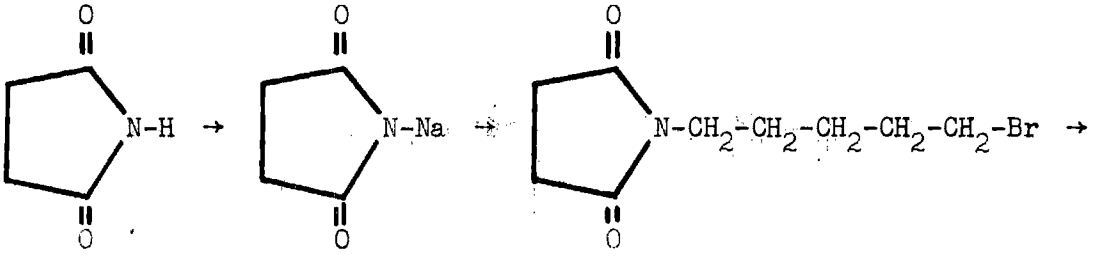
DISCUSSION OF RESULTS

A synthesis of 1-succinimido-5-hydroxylaminopentane, XXIII, was desirable so that the identity or non-identity of the compound with

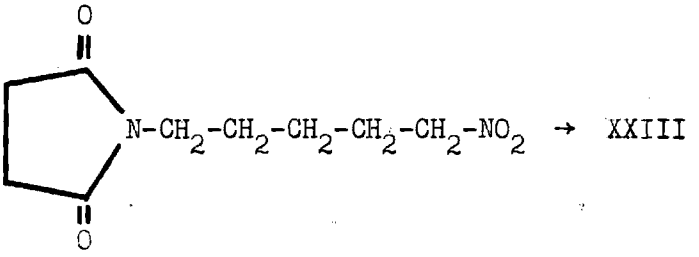


XXIII

authentic nocardamine could be determined. The proposed synthetic sequence is shown below.



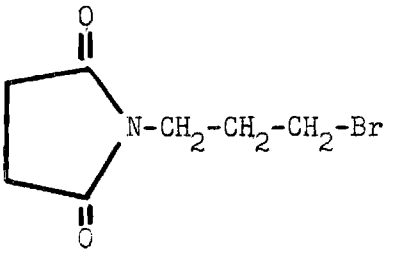
XXIV



XXV

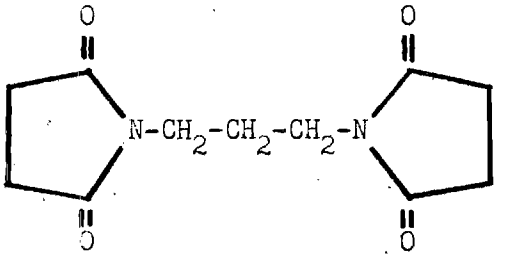
Sodium succinimide was prepared by the reaction of succinimide with sodium ethoxide in ethyl alcohol. This material had been made in a similar manner previously (23), but had not been isolated as a dry solid. An infrared spectrum of the compound showed characteristic succinimide carbonyl absorptions at 5.65 and 5.88 μ.

As a model reaction for the preparation of 1-succinimido-5-bromopentane, XXIV, the reported preparation (23) of 1-succinimido-3-bromopropane, XXVI, was repeated; a mixture of sodium succinimide and two molar



XXVII

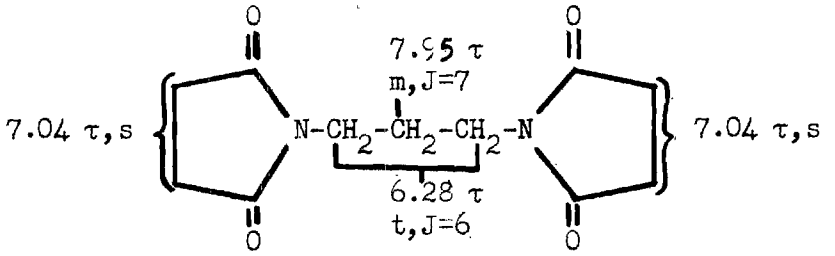
equivalents of 1,3-dibromopropane was boiled under reflux overnight. There could be isolated from the gummy reaction product only 1,3-bis-succinimidopropane, XXVII. The analytical data were consistent with the formula $C_{11}H_{14}N_2O_4$ for the compound. The infrared spectrum of XXVII



XXVII

showed typical succinimido carbonyl bands at 5.63 and 5.86 μ. The

information obtained from a nuclear magnetic resonance spectrum of a trifluoroacetic acid solution of the compound is shown below. The small

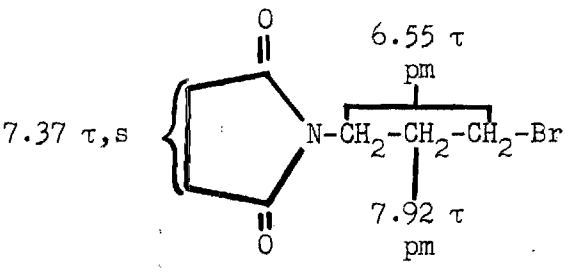


XXVII

letters refer to the multiplicity of the peaks (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, pm = poorly resolved multiplet). The coupling constant, J, is given in cycles per second. As indicated, the eight equivalent protons in the succinimido portions of the molecule appeared as a singlet at 7.04 τ. The four protons of the two methylene groups which are attached to nitrogen appeared as a triplet at 6.28 τ, and the two protons of the methylene group which is bonded only to carbon appeared as a quintet at 7.95 τ.

1-Succinimido-3-bromopentane (XXVI) was successfully prepared by the reaction of sodium succinimide with five molar equivalents of 1,3-dibromopropane in acetone solution. The infrared spectrum of XXVI showed the usual succinimido carbonyl absorption at 5.65 and 5.86 μ. The assignments of the peaks observed in the nuclear magnetic resonance spectrum of a carbon tetrachloride solution of the compound are shown below. As previously observed, the protons of the succinimido moiety appeared as a singlet [the line position (7.37 τ) is shifted upfield relative to that observed in the similar XXVII (7.04 τ) because of the change in

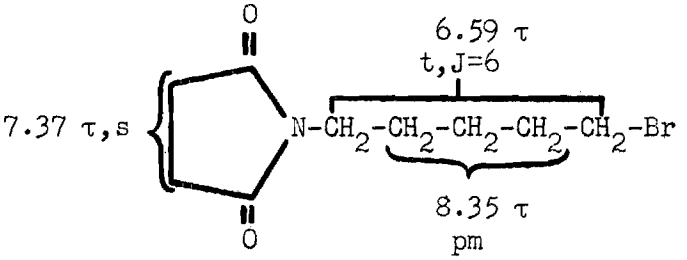
solvent]. The protons of the methylene group attached to nitrogen and



XXVI

those of the methylene group bonded to bromine appeared as a complex multiplet at 6.55 τ. The protons of the methylene group which are bonded only to carbon appeared as a poorly resolved multiplet at 7.92 τ.

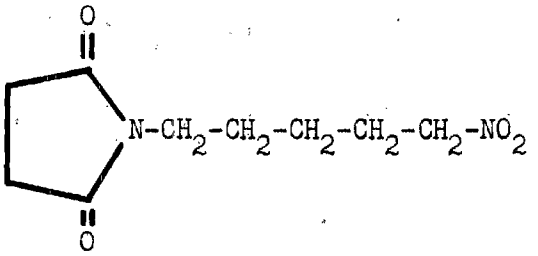
1-Succinimido-5-bromopentane (XXIV) could be obtained by the similar reaction of sodium succinimide with 1,5-dibromopentane in acetone solution, but the reaction resulted in a better yield of XXIV when N, N-dimethylformamide was used as the solvent. The infrared spectrum of XXIV showed the expected absorption at 5.64 and 5.88 μ. The data obtained from a nuclear magnetic resonance spectrum of a carbon tetrachloride solution of the compound are shown below.



XXIV

The preparation of 1-succinimido-5-nitropentane, XXV, was next

undertaken. In an effort to prepare the model compound 1-succinimido-3-nitropropane, 1-succinimido-3-bromopropane (XXVI) was allowed to react

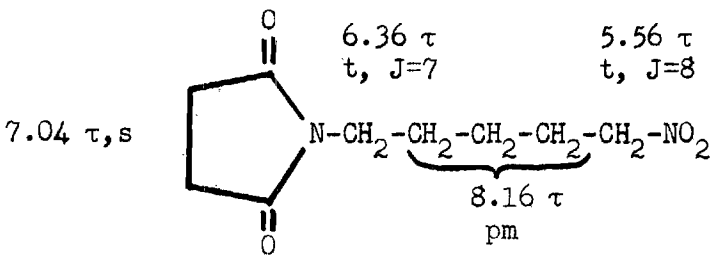


XXV

with silver nitrite in 1-nitropropane solution. The conditions employed had been used successfully for the conversion of 1-phthalimido-5-bromopentane into 1-phthalimido-5-nitropentane (30). In that case (30), however, there had been no indication of the yield or the purity of the product; the crude material was used in a subsequent reaction. The reaction of XXVI with silver nitrite did not appear to produce 1-succinimido-3-nitropropane. An infrared spectrum of the crude product showed bands at 5.62, 5.88, and 6.10 μ; there was no absorption near 6.45 μ - the wavelength most diagnostic of alkyl nitro groups (33). The band at 6.10 μ possibly could be attributed to the presence of alkyl nitrite, which reportedly (34) would absorb near 6.00 μ.

1-Succinimido-5-nitropentane (XXV) was successfully prepared by the reaction of 1-succinimido-5-bromopentane (XXIV) with sodium nitrite in dimethylsulfoxide solution - a procedure recommended by Kornblum and Powers (35) for the conversion of primary alkyl halides into the corresponding nitro compounds. The reaction was allowed to proceed at room temperature for two hours. This reaction was chosen on the basis of a previous preparation in which aliquots of the reaction solution were

withdrawn after 2, 4, 5-1/2, 23, and 72 hours. Infrared spectra of the samples were recorded, and the ratio of the intensity of the absorption at 6.48 μ ($-NO_2$) to that at 5.66 μ (succinimido C=O) was calculated from the spectrum of each sample. The ratio was greatest for the sample withdrawn after a reaction time of two hours. The extent of reaction was estimated, by isolation as silver bromide, of the bromide ions produced during the reaction; this estimation indicated that the reaction was 91% complete. The crude 1-succinimido-5-nitropentane was purified by distillation <u>in vacuo</u>. However, it was not possible to obtain a good yield of constant boiling material; there were obtained three fractions of approximately equal weight boiling at 169-173°/0.8 mm. (fraction 1), 173-178°/0.8 mm. (fraction 2), and 178-181°/0.8 mm. (fraction 3). The infrared spectrum of fraction 1 showed bands at 5.66, 5.90, and 6.48 μ; it also showed a band of medium intensity at 2.80 μ. The spectrum of fraction 2 showed bands at 2.80 (intensity slightly reduced relative to that of fraction 1), 5.66, 5.90, and 6.48 μ, and that of fraction 3 showed absorptions at 2.80 (weak), 5.66, 5.90, and 6.48 μ. The information obtained from the nuclear magnetic resonance spectrum of a trifluoroacetic acid solution of fraction 3 is indicated below. Fraction 3 was redistilled for analysis; the analytical data were satisfactory.

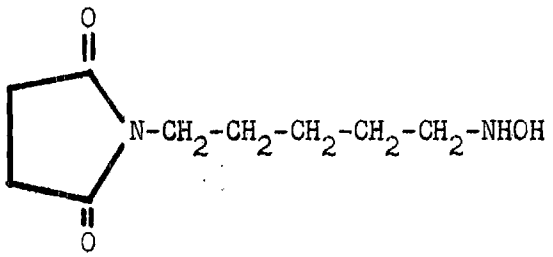


XXV

In some earlier preparations of XXV, distillation of the crude product gave no fraction whose infrared spectrum showed only weak absorption at 2.80 μ; the distillates always showed a band of medium intensity at this wavelength. Analytical data on a sample of one of the higher boiling fractions (b.p. 170°/0.5 mm.) were obtained. The data indicated a carbon content which was 2.5% higher and a nitrogen content which was 1.0% lower than those calculated for $C_9H_{14}O_4N_2$; the hydrogen analysis was satisfactory. It was initially thought that the unexpected infrared absorption at 2.80 μ could be an overtone of the strong carbonyl band at 5.90 μ. However, the unsatisfactory analytical data and the subsequent reduction in intensity of this band by means of fractional distillation made this explanation less acceptable. That the material was composed of 1-succinimido-5-nitropentane contaminated with some 1-succinimido-5-hydroxypentane might be more reasonable. In support of this idea, it was found that the infrared band at 2.80 μ could be considerably reduced in intensity by stirring a chloroform solution of the material with anhydrous calcium chloride. The origin of such 1-succinimido-5-hydroxypentane, however, could not be easily rationalized. A preliminary attempt to produce alcoholic products by the attempted reaction of several alkyl halides in dimethylsulfoxide solution to which a small quantity of water had been added was partially successful (36).

It has been reported in the literature that N-alkylhydroxylamines can be prepared by the hydrogenation of alkyl nitro compounds in the presence of palladium catalyst (37), and that oxalate derivatives of N-alkylhydroxylamines can be prepared by the hydrogenation of alkyl nitro compounds in the presence of oxalic acid using palladium on barium sulfate

as the catalyst (38). The preparation of 1-succinimido-5-hydroxylaminopentane, XXIII, by hydrogenation of 1-succinimido-5-nitropentane

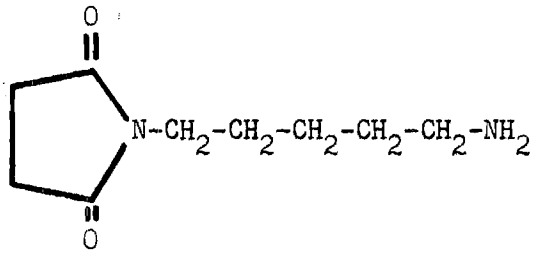


XXIII

(XXV) using each of the reported procedures (37,38) was attempted. When XXV was subjected to hydrogenation using palladium as the catalyst, the compound rapidly absorbed 2.6 molar equivalents of hydrogen. The progress of the reduction was followed by measuring at five-minute intervals the volume of hydrogen which had been absorbed. A plot of the volume of hydrogen absorbed versus time showed no decrease in the rate of hydrogenation until a volume of hydrogen equivalent to 2.3 moles per mole of XXV had been taken up. Successful hydrogenation of an alkyl nitro compound to an alkylhydroxylamine would presumably require that the rate of reduction of the nitro group to the hydroxylamino group be greater than the rate of further reduction of the hydroxylamino group, i.e., the reduction should either stop or show a reasonable decrease in rate after the absorption of two moles of hydrogen per mole of nitro compound.

That the product of hydrogenation of XXV was not XXIII was further indicated by the fact that the material showed no reducing properties, e.g., it gave negative color tests with Benedict's, Fehling's, and Tollen's reagents. The compound gave a purple color, characteristic of amines,with

ninhydrin reagent. That the product was homogeneous was shown by the fact that it yielded only one spot on paper chromatography in two solvent systems, R_F 0.54 (BAW) and 0.62 (BH) The infrared spectrum of the compound showed bands at 2.95 μ (broad, amino N-H) and at 5.65 and 5.90 μ (succinimido C=O). This product appears to be 1-succinimido-5-aminopentane, XXVIII.

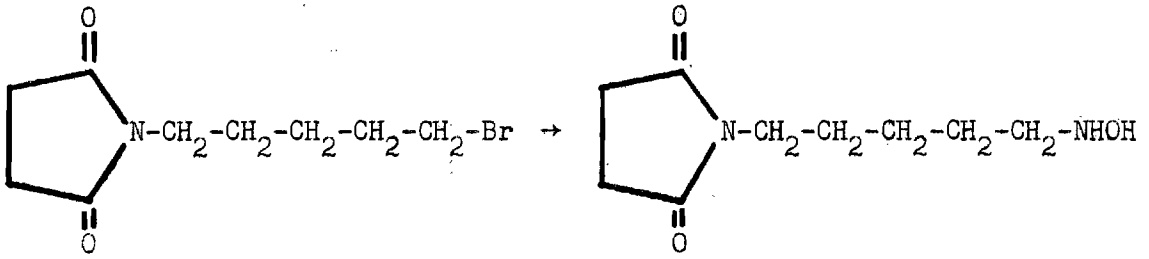


XXVIII

Similar hydrogenations of XXV using platinum or palladium on barium sulfate as the catalyst proceeded in a like manner. When hydrogenation of XXV was attempted in the presence of a 0.50 molar quantity of oxalic acid using palladium on barium sulfate as the catalyst, no hydrogen was absorbed by the sample.

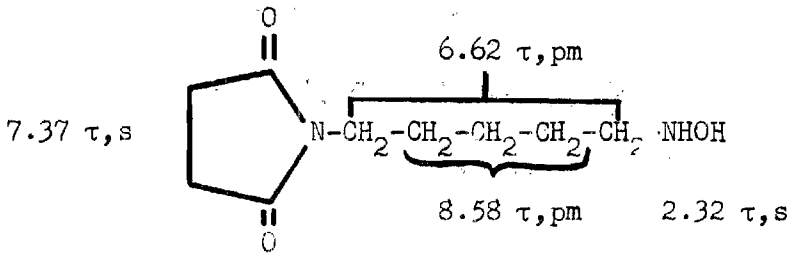
An alternate route to 1-succinimido-5-hydroxylaminopentane (XXIII) was thus required. Reports had appeared in the literature (6,39) that the reaction of certain n-alkyl halides with hydroxylamine produced the corresponding n-alkylhydroxylamines. A direct conversion of 1-succinimido-5-bromopentane (XXIV) into 1-succinimido-5-hydroxylaminopentane (XXIII), therefore, seemed possible. XXIV was allowed to react with hydroxylamine in methyl alcohol solution, and the reaction did produce a low yield of XXIII. The product was a clear gum which resisted attempts to induce its solidification. It was purified by silicic acid chromatography. An

infrared spectrum of the material showed bands at 2.83 and 2.90 μ (shoulder) (hydroxylamino N-H and -OH) and at 5.63 and 5.89 μ (succinimido C=O). Assignment of the peaks observed in the nuclear magnetic resonance



XXIV XXIII

spectrum of a carbon tetrachloride solution of XXIII is shown below. Paper chromatography of XXIII in BH yielded two spots, R_F 0.34 (hydroxylamine) and 0.68 (1-succinimido-5-hydroxylaminopentane). The reported R_F value in BH for naturally derived 1-succinimido-5-hydroxylaminopentane, which had been obtained and characterized by other workers (8) while this work was in progress, is 0.70.

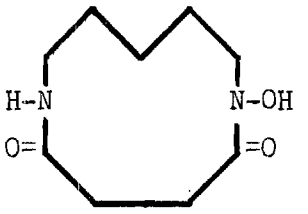


XXIII

Hydrogenation of XXIII gave an oil whose behavior on paper chromatography was identical to that of the previously discussed XXVIII, i.e., it yielded only one spot on paper chromatography in two solvent systems, R_F 0.55 (BAW) and 0.62 (BH).

In an effort to characterize XXIII better, a solid oxalate derivative of the material was prepared. The derivative was amorphous, however, and crystallization of it was not successful. An infrared spectrum of the oxalate showed the usual succinimido carbonyl bands at 5.63 and 5.89 μ, and paper chromatography of the material yielded only one spot. The analytical data, however, were not satisfactory.

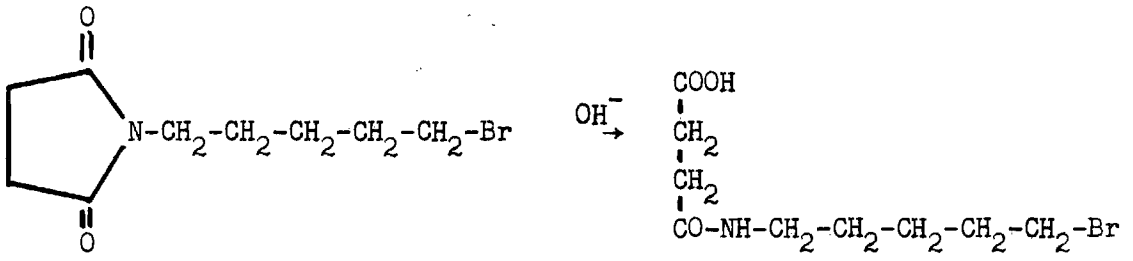
It had become apparent by this time that 1-succinimido-5-hydroxylaminopentane was not identical to nocardamine. A sample of authentic nocardamine had been obtained from Dr. J. Renz of the Sandoz Laboratories, Basel, Switzerland. The material melted at 174-177° [lit. (1) 184°]. The infrared spectrum of nocardamine showed important bands at 2.95 (amide N-H), 6.17 (amide C=O), and 6.46 μ (amide N-H); there was no absorption from 5.50-6.00 μ. The nuclear magnetic resonance spectrum of a trifluoroacetic acid solution of nocardamine was complex but noticeably different than that of XXIII; in particular, it showed no sharp singlet indicative of succinimido-type protons around 7.04 τ. It thus appeared that nocardamine must be identical to 1-hydroxy-1,6-diaza-2,5-dioxocycloundecane, XIII.



XIII

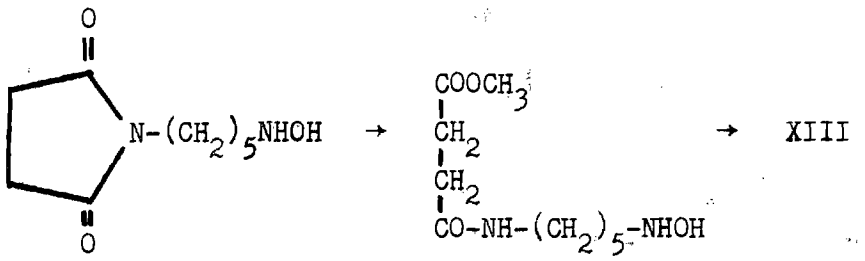
It had been found, in the course of a search for means of separation of 1-succinimido-5-nitropentane (XXV) and the 1-succinimido-5-bromopentane

(XXIV) from which it was obtained, that when XXIV was stirred for five minutes with aqueous potassium hydroxide, it dissolved completely. XXIV could not be removed from the basic aqueous solution by extraction with chloroform. When the aqueous solution was acidified, there could be obtained a 69% yield of 4-oxo-5-aza-10-bromodecanoic acid, XXIX.



XXIV XXIX

The infrared spectrum of XXIX showed bands at 3.80 (carboxylic acid O-H), 5.88 (carboxylic acid C=O), 6.00 (amide C=O), and 6.45 μ (amide N-H). The possibility that 1-succinimido-5-hydroxylaminopentane (XXIII) could be converted into the hydroxylamino ester XXX by the similar action of sodium methoxide in methyl alcohol was investigated. If this conversion

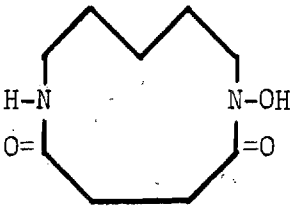


XXIII XXX

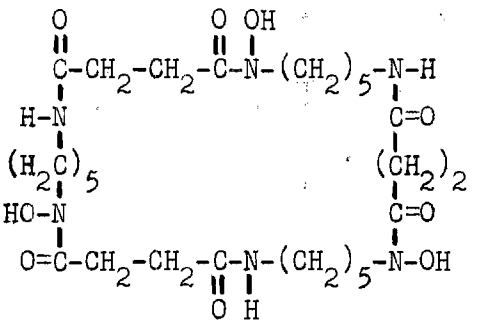
were successful, an attempt to induce cyclization of XXX into 1-hydroxy-1,6-diaza-2,5-dioxocycloundecane (XIII) would be made. In fact, it appeared reasonable that XXX, if formed, might even be converted into XIII under the

conditions of its (XXX) formation, since the most common method of preparation of alkyl hydroxamic acids is the reaction of an ester with hydroxylamine in alcoholic alkoxide solution (40). A sample of 1-succinimido-5-hydroxylaminopentane (XXIII) was added to a solution of sodium methoxide in methyl alcohol. Aliquots of the solution were withdrawn after 1, 3-1/2, 7-1/2, and 24 hours, and compared by means of paper chromatography with XXIII. Each of the samples, including XXIII, showed only one identical spot.

Near the completion of the work leading to the synthesis of 1-succinimido-5-hydroxylaminopentane, the conflicting reports (6,10,12) concerning the molecular weight of nocardamine had appeared in the literature. A choice between the structures 1-hydroxy-1,6-diaza-2,5-dioxocycloundecane, XIII, and 1,12,23-trihydroxy-1,7,12,18,23,29-hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane, XVI, was thus made uncertain.

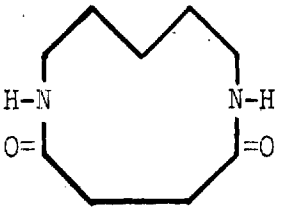


XIII

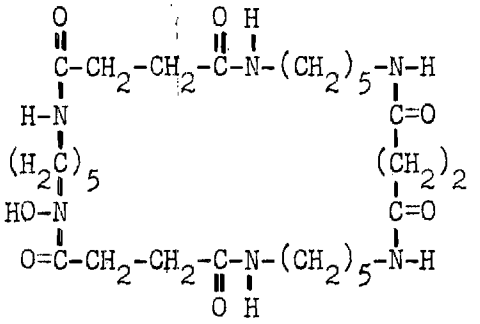


XVI

The resolution of this problem by determining the identity or non-identity of the cyclic polyamide obtained by reduction of authentic nocardamine with synthetic samples of 1,6-diaza-2,5-dioxocycloundecane, XVIII, and 1,7,12,18,23,29-hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane, XXI, was undertaken.



XVIII

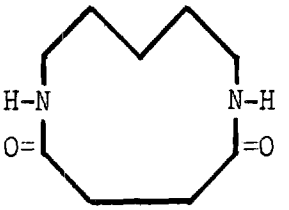


XXI

A sample of authentic nocardamine was hydrogenated at room temperature and atmospheric pressure using Raney nickel as the catalyst. The product, XXXII, melted at 279-281° [lit. (12) 273°] after three recrystallizations from n-butyl alcohol. The analytical data on XXXII were consistent with the empirical formula $C_9H_{16}N_2O_2$. The nuclear magnetic resonance spectrum of a trifluoroacetic acid solution of the compound was in agreement with either of the structures XVIII or XXI. The spectrum is reproduced in Figure 2. The protons of the succinic acid residue(s)

appeared as a singlet at 7.04 τ, those of the methylene groups adjacent to nitrogen as a poorly resolved multiplet at 6.50 τ, and those of the methylene groups attached only to other methylene groups as a poorly resolved multiplet at 8.33 τ. The amide protons appeared as a singlet at 1.82 τ. The infrared spectrum of XXXII showed important absorptions at 3.07 (amide N-H), 6.10 (amide C=O), and 6.47 μ (amide N-H); the spectrum is reproduced in Figure 1. It had been hoped that the molecular weight of the compound could be measured by means of a Vapor Pressure Osmometer. However, XXXII was too insoluble in water and in the usual organic solvents which may be used with the instrument for this determination to be made. The only solvent in which the compound was found to be reasonably soluble was trifluoroacetic acid.

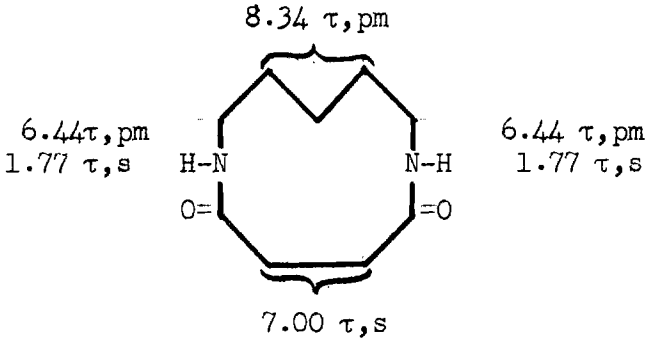
1,6-Diaza-2,5-dioxocycloundecane, XVIII, was prepared by the reaction of succinyl chloride with 1,5-pentanediamine. The procedure employed



XVIII

had been used successfully by Stetter and Marx (13) for the preparation of a number of similar macrocyclic diamides. XVIII was purified for analysis by sublimation <u>in vacuo</u>. The analytical data were consistent with the formula $C_9H_{16}N_2O_2$. The compound melted at 218-221° (dec.). The nuclear magnetic resonance spectrum of a trifluoroacetic acid solution of XVIII is reproduced in Figure 4; the assignment of peaks is shown below.

The infrared spectrum of XVIII showed important bands at 3.05 (amide N-H),



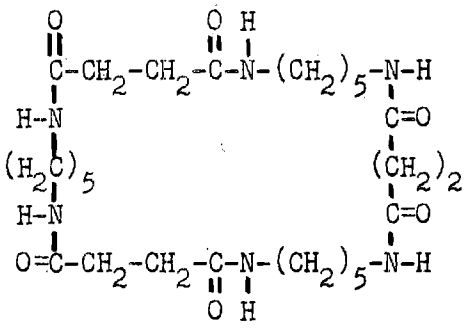
XVIII

6.10 (amide C=O), and 6.47 μ (amide N-H); the spectrum is reproduced in Figure 3. The molecular weight of XVIII was measured using a Vapor Pressure Osmometer. The observed molecular weights of the compound were 179 ± 11, 189 ± 5, and 173 ± 11 (calc'd. for $C_9H_{16}N_2O_2$, 184).

A comparison of the physical properties of XVIII and XXXII showed that the two compounds were not identical. The melting point of the reduction product (XXXII) of authentic nocardamine was 279-281°; 1,6-diaza-2,5-dioxocycloundecane (XVIII) melted at 218-221°. XVIII sublimed when heated at atmospheric pressure, but XXXII did not sublime. It can be noted from Figures 1 and 3 that there are marked differences in the infrared spectra of XVIII and XXXII in the region 7.50 to 14.00 μ. There is a significant difference in the solubility in water of XVIII and XXXII. The nuclear magnetic resonance spectra of XVIII and XXXII (Figures 2 and 4) are, as expected, very similar.

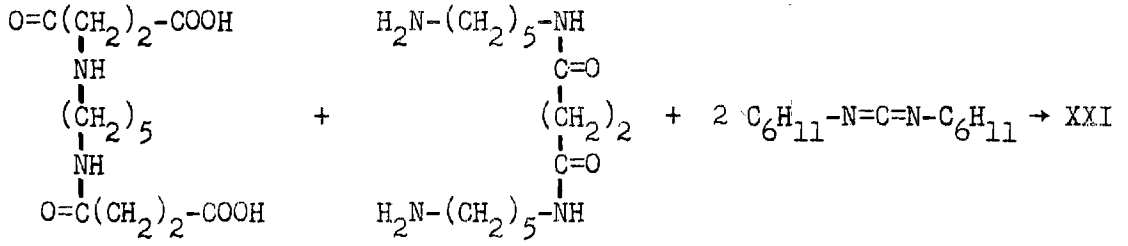
A synthesis of 1,7,12,18,23,29-hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane, XXI, the proposed reduction product of nocardamine, was next undertaken in order to define more exactly the structure of nocardamine.

It was proposed to prepare XXI by a cyclization reaction of synthetic 4,12-dioxo-5,11-diazapentadecanedioic acid, XXXIII, and synthetic



XXI

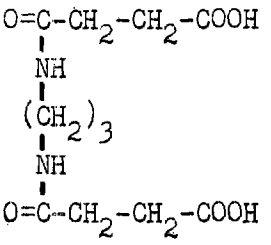
1,15-diamino-6,11-diaza-7,10-dioxohexadecane, XXIV, using two molar equivalents of dicyclohexylcarbodiimide, XXXV.



XXXIII XXIV XXXV

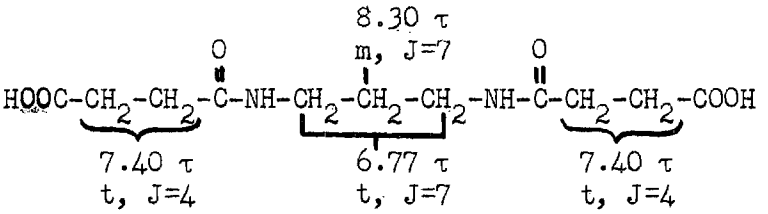
As a model for the preparation of 4,12-dioxo-5,11-diazapentadecanedioic acid (XXXIII), a synthesis of 4,10-dioxo-5,9-diazatridecanedioic acid, XXXVI, was desirable. It was found that XXXVI was produced in good yield when a solution of 1,3-propanediamine in benzene was added to a hot saturated solution of 2.5 molar equivalents of succinic anhydride in benzene. The diacid XXXVI precipitated from the reaction solution and could be obtained in nearly quantitative yield by simple filtration. The compound could be purified by recrystallization from hot water. The

analytical data were consistent with the formula $C_{11}H_{18}N_2O_6$; the neutral-



XXXVI

ization equivalent of the product was 141 (calc'd. for a diacid $C_{11}H_{18}N_2O_6$, 137). The infrared spectrum of XXXVI showed bands at 3.00 (amide N-H), 3.75 (carboxylic acid O-H), 5.94 (carboxylic acid C=O), 6.14 (amide C=O), and 6.55 μ (amide N-H). Assignment of the peaks observed in the nuclear magnetic resonance spectrum of a deuterium oxide solution of the compound is shown below. The eight protons of the succinamic acid portions of the

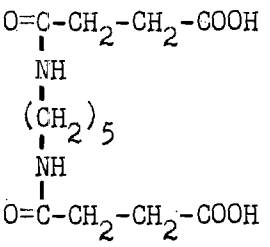


XXXVI

molecule appeared as a triplet at 7.40 τ. The four protons of the two methylene groups adjacent to nitrogen appeared as a triplet at 6.77 τ, and the two protons of the methylene group which is bonded to two other methylene groups appeared as a quintet at 8.30 τ. The exchangeable carboxylic acid and amide protons appeared as a water peak at 5.25 τ.

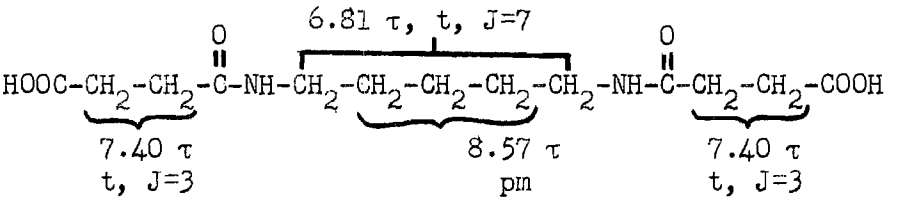
4,12-Dioxo-5,11-diazapentadecanedioic acid, XXXIII, was prepared in 97 percent yield by a similar reaction of succinic anhydride with

1,5-pentanediamine in benzene solution. Analytical data were consistent



XXXIII

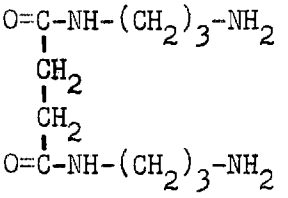
with the formula $C_{13}H_{22}N_2O_6$, and the neutralization equivalent of the compound was 154 (calc'd. for a diacid $C_{13}H_{22}N_2O_6$, 151). The infrared spectrum of XXXIII showed bands at 3.03 (amide N-H), 3.75 (carboxylic acid O-H), 5.93 (carboxylic acid C=O), 6.13 (amide C=O), and 6.55 μ (amide N-H). Assignment of the peaks observed in the nuclear magnetic resonance spectrum of a deuterium oxide solution of the compound is indicated below.



XXXIII

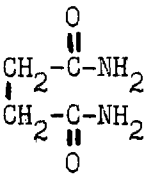
A synthesis of 1,15-diamino-6,11-diaza-7,10-dioxohexadecane (XXXIII) was then required. Several one-step reactions which were designed to produce the model compound 1,12-diamino-4,9-diaza-5,8-dioxododecane, XXXVII, were investigated. It seemed reasonable that the reaction of succinyl chloride with excess 1,3-propanediamine might yield XXXVII. A search of the literature, however, revealed that the reaction of succinyl

chloride with amines sometimes yield butyrolactone derivatives rather

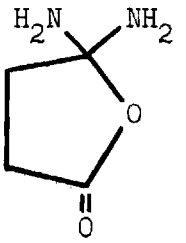


XXXVII

than the expected succinamide derivatives. For example, the reaction of succinyl chloride with ammonia is reported to give only a five per cent yield of succinamide, XXXVIII; the major product is γ,γ-diaminobutyrolactone, XXXIX (41). The reaction of succinyl chloride with methylamine

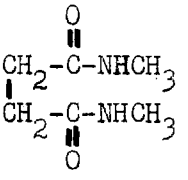


XXXVIII

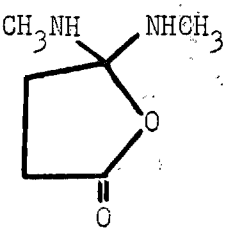


XXXIX

results in a 25 per cent yield of N,N'-dimethylsuccinamide, XL; the major product is butyrolactone derivative XLI (41). The reaction of succinyl chloride with glycine ethyl ester, however, proceeds "normally" to yield the succinamide derivative XLII (42), and the reaction of succinyl chloride

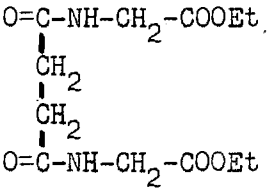


XL

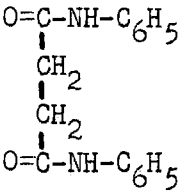


XLI

with aniline gives the succinamide XLIII in 90 per cent yield (41). With the exception of the previously mentioned reports (12,13) of the preparation of cyclic diamides by the reaction of succinyl chloride with 1,5-pen-



XLII



XLIII

tanediamine or 1,6-hexamethylenediamine under high-dilution conditions, no report of a reaction of succinyl chloride with a diamine was found in the literature.

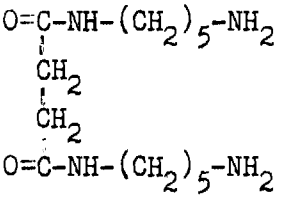
The reaction of succinyl chloride with excess 1,3-propanediamine was investigated. A solution of succinyl chloride in benzene was slowly added to a solution of eight molar equivalents of 1,3-propanediamine in benzene. The white solid product was subjected to paper chromatography in two solvent systems. Only one ninhydrin-positive spot was observed, and it was due to 1,3-propanediamine. The product was not further investigated.

Succinamide can be prepared in good yield by the reaction of diethyl succinate with ammonia (43). Therefore, another reasonable and direct approach to the preparation of 1,12-diamino-4,9-diaza-5,8-dioxododecane (XXXVII) was thought to be the reaction of diethyl succinate with excess 1,3-propanediamine. Diethyl succinate was added to ten molar equivalents of 1,3-propanediamine, and the reaction solution was allowed to stand at room temperature overnight. The reaction mixture contained a white gelatinous solid that was removed by filtration. The

infrared spectrum of the solid showed no absorption from 5.50 to 6.10 μ; this indicated the absence of unreacted diethyl succinate. There was a band at 6.13 μ (amide C=O) in the spectrum of this material. The infrared spectrum of the filtrate showed no absorption from 5.50 to 6.00 μ; there was a band at 6.02 μ (amide C=O). Both the solid residue and the filtrate were subjected to paper chromatography in two solvent systems in an effort to determine the presence or absence of compounds which contained an amino group(s). Each of the samples yielded only one ninhydrin-positive spot, and it was due to 1,3-propanediamine.

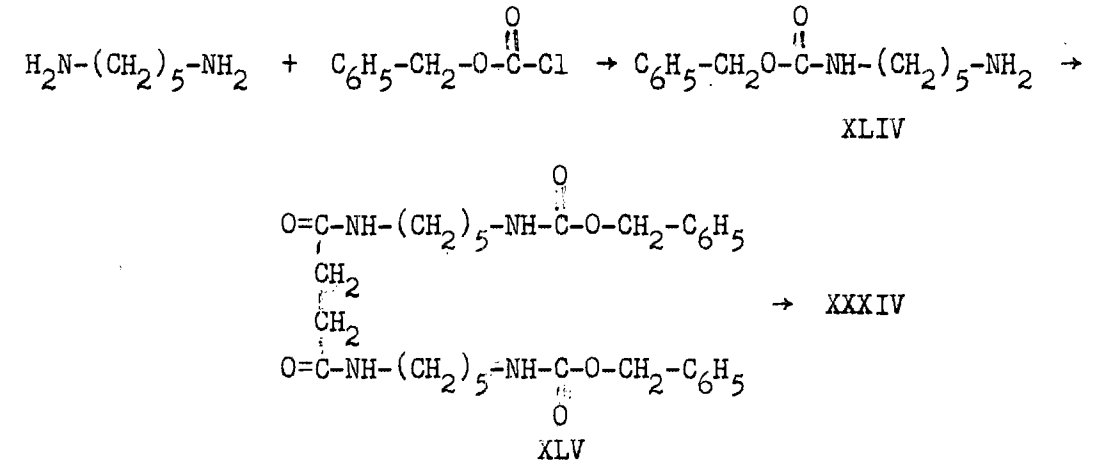
The reaction of diethyl succinate with ten molar equivalents of 1,3-propanediamine in benzene solution was also investigated. Aliquots of the reaction solution were withdrawn after four hours, twenty-two hours, forty-eight hours, and five days. The benzene was removed from the samples, and infrared spectra of the residues were recorded. The spectra of the samples corresponding to reaction times of four, twenty-two, and forty-eight hours showed absorption at 5.76 μ; this indicated that unreacted diethyl succinate remained in the reaction mixture. The spectrum of the sample withdrawn after five days showed no absorption from 5.50 to 6.00 μ; there were bands at 6.05 and 6.34 μ (probably amide C=O and amide N-H, respectively. Examination of the product by means of paper chromatography again indicated that the only amine present was 1,3-propanediamine.

It thus appeared that any preparation of 1,15-diamino-6,11-diaza-7,10-dioxohexadecane, XXXIV, would necessarily require the reaction of a succinic acid derivative with a monofunctional amine (derived from 1,5-pentanediamine) to yield an intermediate amide from which XXXIV could subsequently be generated.



XXXIV

The proposed sequence is shown below. 1-Carbobenzoxyamino-5-aminopentane, XLIV, would be prepared by the reaction of carbobenzoxy chloride with excess 1,5-pentanediamine; XLIV would be allowed to react



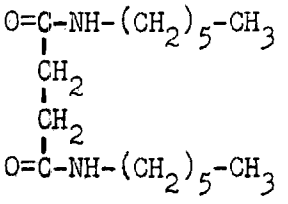
XLIV

XLV

with succinyl chloride to produce 1,15-bis-carbobenzoxyamino-6,11-diaza-7,10-dioxohexadecane, XLV. The carbobenzoxy protecting groups of XLV would then be removed by hydrogenolysis to yield XXXIV.

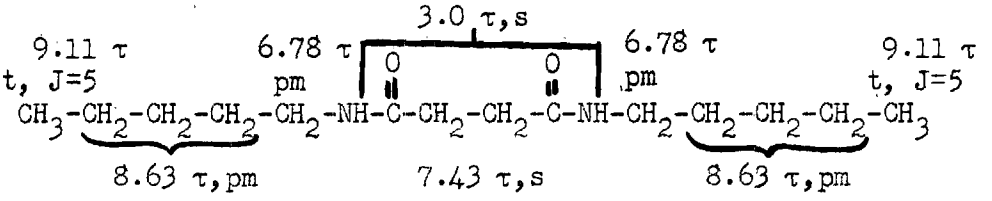
It seemed desirable, in view of the previous results which had been obtained with succinyl chloride, to first study the reaction of succinyl chloride with a model monofunctional alkyl amine. Succinyl chloride was allowed to react with five molar equivalents of 1-amino-pentane in benzene solution. The reaction resulted in a 75 per cent

yield of 6,11-diaza-7,10-dioxohexadecane, XLVI. The infrared spectrum of XLVI showed bands at 2.80 (amide N-H), 2.94 (amide N-H), 6.00 (amide C=O), and 6.55 μ (amide N-H). Assignment of the peaks observed in the



XLVI

nuclear magnetic resonance spectrum of a deuterochloroform solution of XLVI is shown below. For analysis, a sample of the material was sublimed



XLVI

in vacuo; the analytical data were satisfactory.

It was again decided to perform preliminary work on the new reaction sequence with 1,3-propanediamine rather than the less available 1,5-pentanediamine. A preparation of 1-carbobenzoxyamino-3-aminopropane was first undertaken.

An unexpected problem associated with the use of the commercially available carbobenzoxy chloride (Columbia Organic Chemicals Company material) was initially encountered. A nuclear magnetic resonance spectrum of a carbon tetrachloride solution of the material, as received, showed peaks at 2.76 τ (pm), 4.78 τ (s, 3.5 integration units), 4.87 τ

(s, 1.2 integration units), 5.48 τ (s, 4.2 integration units), and 7.67 τ (s, 1.1 integration units). It had been anticipated that the spectrum of the compound would show only two peaks - one corresponding to the aromatic protons and one to the methylene protons. So it appeared that the commercial carbobenzoxy chloride was grossly impure, and further work with such material was not indicated.

In an attempt to determine the nature of the impurities, nuclear magnetic resonance spectra of several similar compounds were examined. The spectrum of toluene (neat liquid) showed peaks at 2.97 τ (pm, aromatic protons) and 7.87 τ (s, methyl protons). The spectrum of benzyl chloride (carbon tetrachloride solution) showed peaks at 2.74 τ (s, aromatic protons) and 5.52 τ (s, methylene protons), and that of benzal chloride (carbon tetrachloride solution) showed peaks at 2.57 τ (pm, aromatic protons) and 3.37 τ (s, methylene protons). It thus appeared that two of the impurities in the commercial carbobenzoxy chloride were toluene [note the correspondence of peaks at 7.87 τ (neat liquid) in the spectrum of toluene and 7.67 τ (carbon tetrachloride solution) in that of commercial carbobenzoxy chloride] and benzyl chloride (5.52 τ in the spectrum of benzyl chloride and 5.48 τ in that of commercial carbobenzoxy chloride). There apparently was no benzal chloride in the commercial material. The peak at 4.78 τ in the spectrum of the commercial carbobenzoxy chloride was thought to correspond to the methylene protons of carbobenzoxy chloride. The material corresponding to the peak at 4.87 τ is not known.

The commercial carbobenzoxy chloride preparation was purified by distillation <u>in vacuo</u>. A portion of the material was distilled at 0.3-4.0 mm. using a bath temperature of 70°; approximately equal volumes

of distillate and residue were obtained. The nuclear magnetic resonance spectrum of the distillate showed peaks at 2.76 τ (pm, aromatic protons), 4.78 τ (s, 1.7 integration units, methylene protons of carbobenzoxy chloride), 5.49 τ (s, 7.2 integration units, methylene protons of benzyl chloride), and 7.67 τ (s, 2.1 integration units, methyl protons of toluene). A calculation of the relative concentrations of the compounds in the distillate could be made using the integration data. The calculation indicated that the distillate was composed of 17 per cent carbobenzoxy chloride, 70 per cent benzyl chloride, and 13 per cent toluene.

The nuclear magnetic resonance spectrum of the residue showed peaks at 2.75 τ (pm, aromatic protons), 4.77 τ (s, 7.3 integration units, methylene protons of carbobenzoxy chloride), 4.89 τ (s, 3.5 integration units, no assignment made), and 5.49 τ (s, 1.2 integration units, methylene protons of benzyl chloride). A calculation of the relative concentrations of the compounds in the residue indicated 61 per cent carbobenzoxy chloride, 10 per cent benzyl chloride, and 29 per cent "unknown" material. It was assumed that the peak at 4.89 τ ("unknown" material) corresponded to two protons.

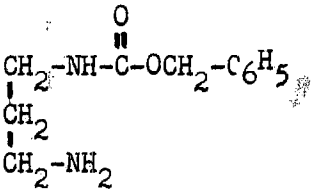
An enrichment in carbobenzoxy chloride by removal of the more volatile benzyl chloride and toluene from the crude preparation was apparent. A calculation of the composition of the commercial carbobenzoxy chloride, as received, indicated 37 per cent carbobenzoxy chloride, 44 per cent benzyl chloride, 7 per cent toluene, and 13 per cent "unknown" material.

On one occasion, very careful distillation of a small portion of the commercial material gave a 20 per cent yield of pure carbobenzoxy

chloride, b.p. 83-85°/3 mm. The nuclear magnetic resonance spectrum of this material showed peaks at 2.67 τ (s, aromatic protons) and 4.78 τ (s, methylene protons).

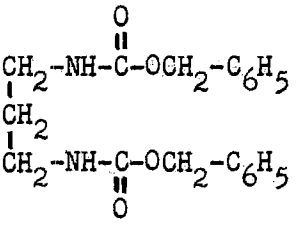
The carbobenzoxy chloride from a different commercial source (Nutritional Biochemicals Corporation material) was, as received, composed of 81 per cent carbobenzoxy chloride and 19 per cent benzyl chloride. This material could be further enriched in carbobenzoxy chloride by removal of most of the benzyl chloride by distillation *in vacuo*. Material from this source was used in all the reactions discussed below.

In an effort to prepare the model compound 1-carbobenzoxyamino-3-aminopropane, XLVII, carbobenzoxy chloride was allowed to react with



XLVII

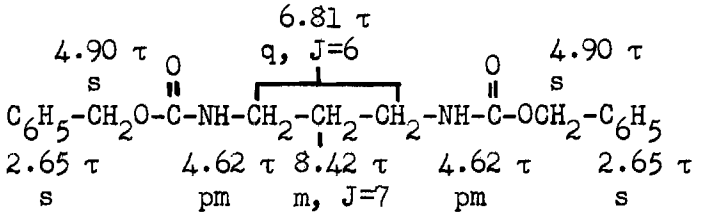
1,3-propanediamine under the usual Schotten-Baumann conditions, *i.e.*, in cold alkaline aqueous solution. The only product isolated was the neutral 1,3-bis-carbobenzoxyaminopropane, XLVIII. The analytical data



XLVIII

were in agreement with the formula $C_{19}H_{22}N_2O_4$ for XLVIII. The infrared

spectrum of the compound showed bands at 2.83 (amide N-H), 5.85 (carbobenzoxy C=O), and 6.63 μ (amide N-H). Assignment of the peaks observed in the nuclear magnetic resonance spectrum of a deuterochloroform solution of XLVIII is shown below. That XLVIII was the only product of this



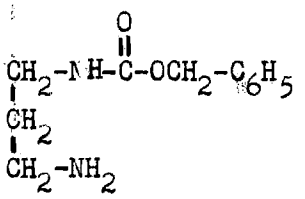
XLVIII

reaction was an unexpected result, but perhaps was a consequence of the heterogeneity of the reaction. Any 1-carbobenzoxyamino-3-aminopropane (XLVII) formed by the heterogeneous reaction of carbobenzoxy chloride with 1,3-propanediamine would be expected to be more soluble in unreacted carbobenzoxy chloride than in the alkaline aqueous solution which contained the 1,3-propanediamine, and extraction of the intermediate XLVII into the carbobenzoxy chloride layer would encourage the further reaction of XLVII with carbobenzoxy chloride to yield XLVIII.

The reaction of carbobenzoxy chloride with 1,3-propanediamine in a homogeneous organic medium was next investigated. A solution of carbobenzoxy chloride in ether was added to a solution of 1,3-propanediamine and triethylamine in ether. The reaction resulted in a 46 per cent yield of 1,3-bis-carbobenzoxyaminopropane (XLVIII); the remainder of the product was a basic liquid whose infrared spectrum showed bands at 2.96 (amino and/or amide N-H), 5.85 (carbobenzoxy C=O), and 6.51 μ (amide N-H). Paper chromatography indicated the presence of two amines in the liquid,

one of which was 1,3-propanediamine.

The results of the above attempts to prepare 1-carbobenzoxyamino-3-aminopentane were not particularly encouraging, but it was decided to proceed with an attempted preparation of 1-carbobenzoxyamino-5-aminopentane, XLIV. A solution of carbobenzoxy chloride in chloroform was



XLIV

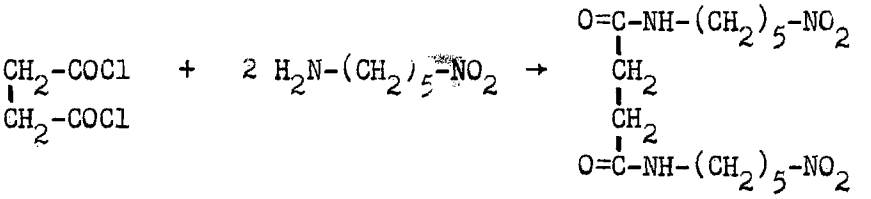
slowly added to a cold solution of three molar equivalents of 1,5-pentanediamine and ten molar equivalents of triethylamine in chloroform. The basic product was a yellow liquid which yielded two ninhydrin-positive spots, neither of which was due to 1,5-pentanediamine, on paper chromatography. The infrared spectrum of the liquid showed bands at 3.00 (amino and/or amide N-H), 5.85 (carbobenzoxy C=O), and 6.52 μ (amide N-H). Distillation <u>in vacuo</u> of a portion of the liquid resulted in the evolution of gas, and the infrared spectrum of the distillate showed no carbonyl absorption. Thus it appeared that, when heated, the material decomposed and yielded carbon dioxide.

A hydrochloride salt of the liquid product was obtained in good yield by the addition of hydrogen chloride gas to an ether solution of the material. The salt was recrystallized from boiling n-butyl alcohol, and paper chromatography of the recrystallized material yielded only one spot. The infrared spectrum of the hydrochloride, however, showed no carbonyl absorption, and the analytical data were not consistent with

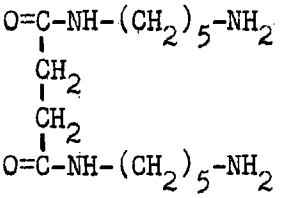
the formula $C_{13}H_{20}N_2O_2 \cdot HCl$ (1-carbobenzoxyamino-5-aminopentane); the analysis indicated the absence of oxygen in the compound. It seems likely that the compound evolved carbon dioxide when recrystallized from the boiling n-butyl alcohol, and the analytical data indicate that the purified salt might be 1-benzylamino-5-aminopentane dihydrochloride, $C_{12}H_{20}N_2 \cdot 2HCl$. The latter, however, is not a known compound, and the synthetic hydrochloride was not further investigated.

An alternate monoamino derivative of 1,5-pentanediamine was thus needed to replace the originally proposed 1-carbobenzoxyamino-5-aminopentane (XLIV) in the reaction sequence leading to a synthesis of 1,15-diamino-6,11-diaza-7,10-dioxohexadecane, XXXIV; 1-amino-5-nitropentane, XLIX, seemed to be a suitable choice.

The revised reaction route is shown below. 1-Amino-5-nitropentane (XLIX) would be generated from the known 1-amino-5-nitropentane hydrochloride (30). XLIX would then be allowed to react with succinyl chloride to yield 1,16-dinitro-6,11-diaza-7,10-dioxohexadecane, L, and XXXIV would be produced by hydrogenation of the nitro groups of L.



L



XXXIV

The reported preparation (30) of 1-amino-5-nitropentane was repeated. No mention of the corresponding free base XLIX, however, had appeared in the literature, and conversion of the hydrochloride to XLIX was required. An aqueous solution of 1-amino-5-nitropentane hydrochloride was made alkaline with sodium bicarbonate and the alkaline solution extracted with chloroform in an effort to obtain the free amine; the chloroform extracts contained no material. An aqueous solution of the hydrochloride was made alkaline to pH 12 with sodium hydroxide and the solution extracted with chloroform; the chloroform extracts again contained no material. 1-Amino-5-nitropentane was successfully generated from the hydrochloride by means of ion exchange with an anion exchange resin. The infrared spectrum of the oily free amine showed bands at 2.86 (amino N-H), 3.05 (amino N-H), and 6.44 μ ($-NO_2$). The material was reasonably soluble in water, ethyl alcohol, and N,N-dimethylformamide, but was essentially insoluble in chloroform, acetone, benzene, ether, and tetrahydrofuran. The solubility behavior of XLIX might be due to its existence as a dipolar ion in which the amino group is protonated and the nitro group is present in the anionic aci form.

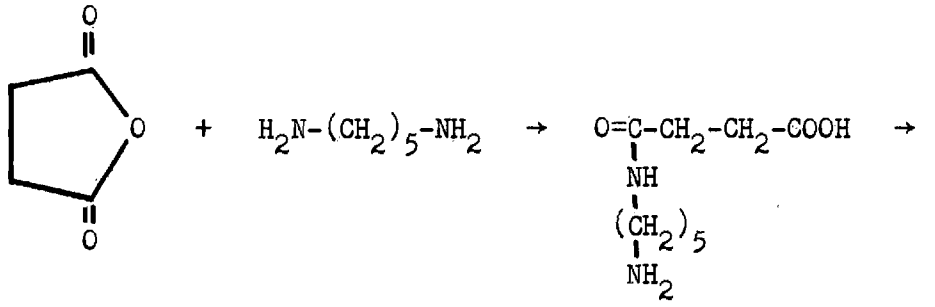
Preparation of 1,16-dinitro-6,11-diaza-7,10-dioxohexadecane (L) by the reaction of succinyl chloride with 1-amino-5-nitropentane was undertaken. The reaction could not be performed homogeneously in benzene solution [as in the successful preparation of 6,11-diaza-7,10-dioxohexadecane (XLVI)], however, because of the insolubility of the amine in benzene. A solution of succinyl chloride in N,N-dimethylformamide was added slowly to a solution of two molar equivalents of 1-amino-5-nitropentane in N,N-dimethylformamide. The neutral product (which was obtained

in poor yield) was a dark brown oil whose infrared spectrum was not consistent with that expected of 1,16-dinitro-6,11-diaza-7,10-dioxohexadecane (L).

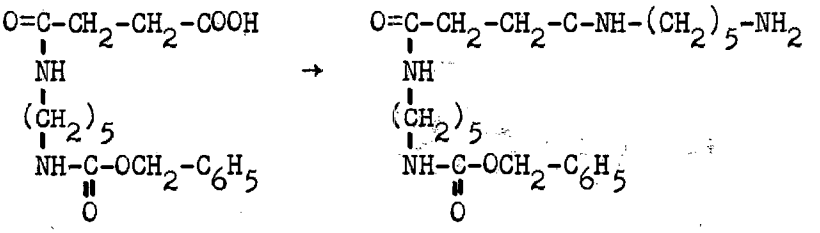
The heterogeneous reaction of succinyl chloride with 1-amino-5-nitropentane in benzene was also investigated. The infrared spectra of the neutral products (which were produced in only poor yield) were not consistent with that expected for L.

No further attempts to prepare a derivative of XXXIV by reaction of an amine with succinyl chloride were made. A synthetic scheme which avoided the use of succinyl chloride or diethyl succinate was conceived; the sequence is shown below. 4-Oxo-5-aza-10-aminodecanoic acid, LI, would be prepared by the reaction of succinic anhydride with excess 1,5-pentanediamine, and LI would be converted by reaction with carbobenzoxy chloride into 4-oxo-5-aza-10-carbobenzoxyaminodecanoic acid, LII. Reaction of LII and excess 1,5-pentanediamine with dicyclohexylcarbodiimide might be expected to produce 1-carbobenzoxyamino-6,11-diaza-7,10-dioxo-16-aminohexadecane, LIII; if this preparation of LIII were successful, hydrogenolytic removal of the carbobenzoxy group of the compound would yield 1,15-diamino-6,11-diaza-7,10-dioxohexadecane, XXXIV. If the conversion of LII to LIII proved unsuccessful, LII and 1-amino-5-nitropentane would be allowed to react with dicyclohexylcarbodiimide to yield 1-carbobenzoxyamino-6,11-diaza-7,10-dioxo-16-nitrohexadecane, LIV. Hydrogenation of LIV would be expected to result in the simultaneous removal of the carbobenzoxy group and reduction of the nitro group to produce XXXIV.

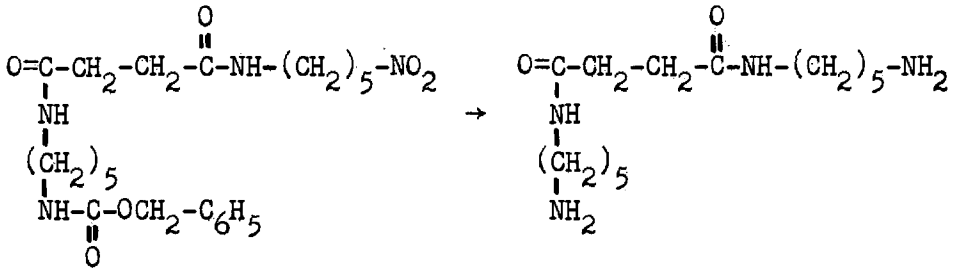
4-Oxo-5-aza-10-aminodecanoic acid, LI, was prepared by the slow



LI



LII LIII



LIV XXXIV

addition of a hot saturated solution of succinic anhydride in benzene to a hot solution of four molar equivalents of 1,5-pentanediamine in benzene. LI was not isolated in pure form; the crude material was dissolved in water and allowed to react with carbobenzoxy chloride under the usual Schotten-Baumann conditions. The product, 4-oxo-5-aza-10-carbobenzoxyaminodecanoic, LII, was a white crystalline solid, m.p.

129-131° after recrystallization from water. The analytical data were consistent with the formula $C_{17}H_{24}N_2O_5$ for LII, and the neutralization equivalent of the compound was 338 (calc'd. for $C_{17}H_{24}N_2O_5$, 336). The infrared spectrum of LII showed bands at 2.81 (amide N-H), 2.92 (amide N-H), 3.73 (carboxylic acid O-H), 5.82 (carboxylic acid C=O and carbobenzoxy C=O), 6.00 (amide C=O), and 6.57 μ (amide N-H).

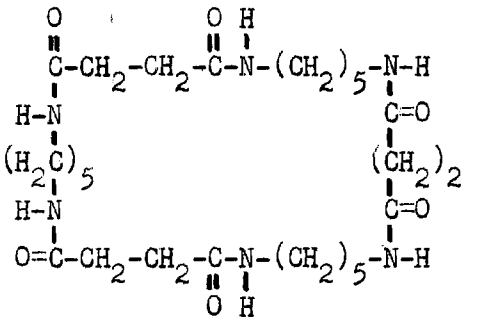
The attempted preparation of 1-carbobenzoxyamino-6,11-diaza-7,10-dioxo-16-aminohexadecane, LIII, by reaction of LII and excess 1,5-pentanediamine with dicyclohexylcarbodiimine resulted in a low (nine per cent) yield of gummy basic material whose infrared spectrum was consistent with that expected for LIII. Paper chromatography of the product yielded only one ninhydrin-positive spot. The gummy product was allowed to react with carbobenzoxy chloride in an effort to produce a solid derivative for characterization purposes; neutral material was obtained in low yield, and was a gum.

The reaction of 4-oxo-5-aza-10-carbobenzoxyaminodecanoic acid (LII) and 1-amino-5-nitropentane with dicyclohexylcarbodiimide in pyridine solution gave an 80 per cent yield of 1-carbobenzoxyamino-6,11-diaza-7,10-dioxo-16-nitrohexadecane (LIV). The analytical data were consistent with the formula $C_{22}H_{34}N_2O_6$ for LIV. The infrared spectrum of the compound showed bands at 2.81 (amide N-H), 2.93 (amide N-H), 5.83 (carbobenzoxy C=O), 6.02 (amide C=O), 6.45 ($-NO_2$), and 6.61 μ (amide N-H).

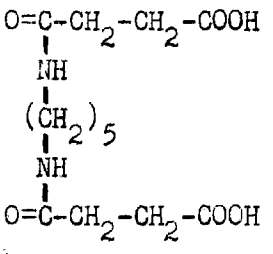
Simultaneous hydrogenolysis of the carbobenzoxy protection group and reduction of the nitro group of 1-carbobenzoxyamino-6,11-diaza-7,10-dioxo-16-nitrohexadecane (LIV) by means of hydrogenation over palladium catalyst yielded 1,15-diamino-6,11-diaza-7,10-dioxohexadecane, XXXIV.

The infrared spectrum of XXXIV showed bands at 2.80 (amino and/or amide N-H), 2.95 (amino and/or amide N-H), 6.02 (amide C=O), and 6.56 μ (amide N-H); there was no absorption near 5.83 (carbobenzoxy C=O) or 6.45 μ ($-NO_2$). Paper chromatography of XXXIV yielded only one spot.

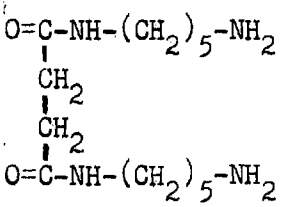
Preparation of 1,7,12,18,23,29-hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane, XXI, was next undertaken. 4,12-Dioxo-5,11-diazapentadecanedioic acid, XXXIII, and 1,15-diamino-6,11-diaza-7,10-dioxohexadecane, XXXIV, were allowed to react with two molar equivalents of dicyclohexylcarbodiimide in N,N-dimethylformamide solution. After a reaction time of two days, an aliquot of the reaction mixture was withdrawn and the solvent removed by distillation in vacuo; the infrared spectrum of the residue showed no absorption near 4.7 μ (-N=C=N-).



XXI



XXXIII



XXXIV

The work-up of the reaction product was based on the known solubility of the reduction product from authentic nocardamine (XXXII) and on the procedure used by Stetter and Marx (13) for the isolation of a number of grossly similar macrocyclic diamides. [By this time, the previously mentioned synthetic work of Prelog and Walser (14) had shown that nocardamine possessed the cyclotritriacontane structure XVI; thus the reduction product from nocardamine, XXXII, was known to be identical to XXI.] The reaction mixture was filtered to separate the material (fraction 1) which was insoluble from that (fraction 2) which was soluble in N,N-dimethylformamide. Fraction 2 was extracted exhaustively with benzene to separate benzene-insoluble polymeric material (fraction 3) from that material (fraction 4) which was soluble in benzene. Fraction 4 was mixed with boiling water to separate the water-insoluble dicyclohexylurea (fraction 5) from that material (fraction 6) which was soluble in hot water.

By design, fraction 6 should have contained any XXI present in the reaction mixture. Fraction 6, however, was a yellow gum which resisted attempts to induce its solidification. Paper chromatographic comparison in two solvent systems of fraction 6 with the reduction product

from authentic nocardamine (XXXII or XXXI) revealed that the fraction contained in it no material of R_F value near that shown by XXXII. Fractions 1 and 3 were also compared with XXXII by means of paper chromatography; there was no material in either of these fractions of R_F value near that of XXXII.

In summary, 1-succinimido-5-hydroxylaminopentane (XXIII) was prepared and found not to be identical to nocardamine. A sample of nocardamine was hydrogenated; the product (XXXII), m.p. 279-281°, was characterized by the analytical data and infrared and nuclear magnetic resonance spectra. An attempt to measure the molecular weight of XXXII using a Vapor Pressure Osmometer was unsuccessful because the material was not sufficiently soluble in the solvents which may be used with the instrument. 1,6-Diaza-2,5-dioxocycloundecane (XVIII) was prepared; the compound, m.p. 218-221°, was characterized by the analytical data, molecular weight, and infrared and nuclear magnetic resonance spectra. A comparison of the physical properties of XVIII and XXXII showed that the two compounds were not identical. A synthesis of 1,7,12,18,23,29-hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane (XXI) was attempted. The required intermediates were prepared and characterized, but the final step of the proposed synthesis - a cyclization reaction of 1,15-diamino-6,11-diaza-7,10-dioxohexadecane (XXIV) and 4,12-dioxo-5,11-diazapentadecanedioic acid (XXXIII) with two molar equivalents of dicyclohexylcarbodiimide - was unsuccessful.

EXPERIMENTAL

Apparatus and Techniques

Unless otherwise indicated, melting points were determined on a Kofler hot stage and are corrected. Microanalyses were performed by Galbraith Laboratories (Knoxville, Tennessee) and Huffman Laboratories (Wheatridge, Colorado). The ion-exchange resins used in this work were regenerated and used as described previously (16). The fraction collector used in the course of column chromatographic separations was a Research Specialties Company Model 1205. Infrared spectra were determined on a Perkin Elmer Model 137 recording spectrophotometer.

The nuclear magnetic resonance spectra were determined on a Varian Model A-60 spectrometer. Reference compounds used and their abbreviations are tetramethylsilane internal standard (TMS) and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS).

The apparatus and techniques used in paper chromatography were the same as those described previously (16). The solvent systems which were most frequently used and their abbreviations are: t-butyl alcohol-acetic acid-water, 2:1:1 (v/v), (BAW); n-butyl alcohol-6 N hydrochloric acid solution, 7:3 (v/v), (BH). Spray reagents which were used most frequently were ninhydrin (17) and 2,3,5-triphenyl-2H-tetrazolium chloride (18).

The following qualitative color tests were used (the method for performing the test is given in the reference cited for the test): ninhydrin (17), ferric chloride (19), Fehling's (20), Tollen's (21), and

Benedict's (22).

A Mechrolab Model 301A Vapor Pressure Osmometer was used for the measurements of molecular weight. The instrument was calibrated for measurements in aqueous solution by means of standard aqueous solutions of sodium chloride (J. T. Baker and Company Analyzed Reagent material, used as received). Triplicate measurements were made. The calibration data are shown in Table 1. A graph of molality versus ΔR was plotted

Table 1. ΔR Values of Standard Sodium Chloride Solutions

Molality of NaCl Solutions	ΔR
0.0000	0.00
0.006941	0.45 ± 0.10
0.01014	0.64 ± 0.08
0.01342	0.79 ± 0.03
0.01717	1.24 ± 0.02
0.02077	1.51 ± 0.04
0.02280	1.52 ± 0.01
0.02346	1.55 ± 0.03
0.02983	1.99 ± 0.01
0.03078	2.06 ± 0.01
0.03196	1.99 ± 0.03

using the above data. The curve which best fit the data was a straight line which passed through six of the points; there were three points slightly above and two points slightly below the line. Aqueous solutions of carefully determined concentration (weight of compound per weight of water) of the compound of unknown molecular weight were prepared, ΔR measured, and the molality of the solution read from the calibration curve.

Synthesis of 1-Succinimido-5-hydroxylaminopentane

Sodium Succinimide

To 2300 ml. of ethyl alcohol (freshly distilled from magnesium turnings was added 21.0 g. (0.910 g. atoms) of freshly pressed sodium ribbon. When the evolution of gas had ceased, the cloudy solution was filtered with suction. The clear filtrate was added to a solution of 90.3 g. (0.910 mole) of succinimide (Eastman Kodak White Label material, used as received) in 1800 ml. of ethyl alcohol (freshly distilled from magnesium turnings). The ethyl alcohol was removed from the solution on a rotating evaporator at reduced pressure until the volume of the resulting mixture was ca. 200 ml. The mixture was filtered with suction and the residue washed with two 100-ml. portions of boiling acetone (dried over potassium carbonate and freshly distilled from potassium permanganate) to yield 93.7 g., 86%, of white solid sodium succinimide. An infrared spectrum of a Nujol mull of the product was recorded and showed $\lambda_{max.}$ at 5.65 and 5.88 μ, among others.

1-Succinimido-3-bromopropane

To a boiling, mechanically stirred solution of 40.40 g. (0.2000 mole) of redistilled 1,3-dibromopropane (b.p. 164-165°) in 500 ml. of acetone (dried over potassium carbonate and freshly distilled from potassium permanganate) was added in ten equal portions over a five-hour period 12.10 g. (0.1000 mole) of sodium succinimide. The reaction mixture was boiled under reflux with stirring for 16 hr., cooled to room temperature, and filtered with suction to remove sodium bromide. The

acetone was removed from the filtrate on a rotating evaporator at reduced pressure, and the residue was freed of excess 1,3-dibromopropane by steam distillation. The water was removed from the distillation residue on a rotating evaporator at reduced pressure. To the residual gum was added 25 ml. of cold water; the sum solidified. The mixture was filtered with suction to yield 9.50 g. of a brown solid. This material was extracted continuously for three days with petroleum ether (b.p. 30-60°) in a Soxhlet extraction apparatus. The petroleum ether was removed from the extract by distillation at atmospheric pressure to yield 4.00 g., 18%, of white crystals, m.p. 53-54°. An infrared spectrum of a chloroform solution of the product was recorded and showed $\lambda_{max.}$ at 5.65 and 5.86 μ, among others. A nuclear magnetic resonance spectrum of the compound in carbon tetrachloride (TMS) was recorded and showed peaks at 6.55 τ (complex multiplet), 7.37 τ (singlet), and 7.92 τ (poorly resolved multiplet). For analysis, a portion of the product was recrystallized three times from light petroleum ether to yield white crystals, m.p. 53-54° [lit. (23) 51-52°].

Anal.	$C_7H_{10}BrNO_2$	Calc'd: C, 38.08; H, 4.57; N, 6.35
	(220.08)	Found : C, 37.75; H, 4.61; N, 5.68

Repetition of the reported preparation of 1-succinimido-3-bromopropane (23) resulted in the isolation of a yellow gum which was insoluble in light petroleum ether. This material was crystallized from ethyl alcohol to give a 30% yield of white crystals, m.p. 201-202°. An infrared spectrum of a chloroform solution of the product was recorded and showed $\lambda_{max.}$ at 5.63 and 5.86 μ, among others. A nuclear magnetic resonance spectrum of the compound in trifluoroacetic acid (TMS) was

recorded and showed peaks at 6.28 τ (triplet, J=6 cps.), 7.04 τ (singlet), and 7.95 τ (quintet, J=7 cps.). For analysis, a portion of the product was recrystallized three times from ethyl alcohol to yield white crystals, m.p. 201-202°.

Anal. $C_{11}H_{14}N_2O_4$ (238.24) Calc'd: C, 55.45; H, 5.92; N, 11.76
Found : C, 55.37; H, 5.86; N, 11.79

1-Succinimido-5-bromopentane

To a mechanically stirred solution of 575 g. (2.50 mole) of redistilled 1,5-dibromopentane (b.p. 111-113°/30 mm.) in 2000 ml. of redistilled N,N-dimethylformamide (b.p. 150-152°) was added in four equal portions over a four-hour period 151 g. (1.25 mole) of sodium succinimide. The reaction mixture was heated under reflux with stirring on a steam bath for 14 hr., cooled to room temperature, and filtered with suction to remove sodium bromide. To the filtrate were added 1500 ml. of chloroform and 5000 ml. of water. The organic layer was drawn off and the aqueous layer extracted with three 500-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure. The residual oil was distilled *in vacuo* through a spinning-band column, and after removal of the remaining N,N-dimethylformamide at 30°/2 mm. and the excess 1,5-dibromopentane at 60°/0.4 mm., there was obtained a fraction boiling at 150-155°/1mm., yield 172 g., 56%. An infrared spectrum of a liquid film of the product was recorded and showed $\lambda_{max.}$ at 5.64 and 5.88 μ, among others. A nuclear magnetic resonance spectrum of the compound in carbon tetrachloride (TMS) was recorded and showed peaks at 6.59 τ (triplet, J=6 cps.), 7.37 τ

(singlet;, and 8.35 τ (poorly resolved multiplet). For analysis, a small portion of the product was redistilled through a spinning-band column, b.p. 150°/0.3 mm., n_D^{28} 1.5150.

Anal. $C_9H_{14}BrNO_2$ Calc'd: C, 43.56; H, 5.69; N, 5.65; Br, 32.21
(248.27) Found : C, 44.18; H, 6.34; N, 5.46; Br, 31.65

4-Oxo-5-aza-10-bromodecanoic Acid

To 25 ml. (0.025 mole) of 1.0 N potassium hydroxide solution was added 1.268 g. (0.005570 mole) of 1-succinimido-5-bromopentane. The mixture was stirred magnetically for five minutes, at which time solution was complete. The solution was extracted with three 20-ml. portions of chloroform. The aqueous portion was cooled in an ice bath and acidified to pH 1 by the dropwise addition of 1 N hydrochloric acid solution. The cold acidic solution was filtered with suction to yield 0.715 g. of a white solid, m.p. 70-72°. The filtrate was extracted with three 20-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure to yield an additional 0.314 g. of the white solid product. The total yield was 1.029 g., 69%. An infrared spectrum of a chloroform solution of the compound was recorded and showed $\lambda_{max.}$ at 3.80, 5.88, 6.00, and 6.54 μ, among others. For analysis, a portion of the material was recrystallized three times from toluene to give white crystals, m.p. 70-71°.

Anal. $C_9H_{16}BrO_3N$ Calc'd: C, 40.61; H, 6.06; N, 5.26
(266.15) Found : C, 40.96; H, 6.06; N, 5.19

1-Succinimido-5-nitropentane

To a solution of 12.00 g. (0.04840 mole) of 1-succinimido-5-bromopentane in 250 ml. of dimethylsulfoxide (J. T. Baker and Company Reagent material, used as received) was added 6.69 g. (0.0965 mole) of sodium nitrite (recrystallized three times from water and dried *in vacuo* over calcium chloride. The reaction mixture was stirred magnetically for five minutes to dissolve the sodium nitrite, and allowed to stand at room temperature for two hours. To the reaction solution were added 125 ml. of chloroform and 600 ml. of water. The organic layer was drawn off and the aqueous layer was extracted with three 50-ml. portions of chloroform.

To the combined aqueous extracts was added 21.2 g. (0.125 mole) of crystalline silver nitrate (J. T. Baker and Company Reagent material, used as received). The resulting mixture was filtered with suction. The solid residue was mixed with 100 ml. of 1:1 nitric acid solution and the mixture boiled for 10 min. The mixture was cooled to room temperature, filtered with suction, and the residue washed successively with two 25-ml. portions of water and two 25-ml. portions of ethyl alcohol. The residual silver bromide was dried *in vacuo* over calcium chloride, yield 8.27 g., 91%.

The combined organic extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure. The residual oil was distilled *in vacuo* through a Vigreux column to obtain fractions boiling at 169-173°/0.8 mm., 173-178°/0.8 mm., and 178-181°/0.8 mm. (fraction 3). The total yield 6.03 g., 56%. The yield of fraction 3 was 2.261 g., 21%. Fraction 3 was redistilled for analysis, b.p. 178°/0.5 mm.

Anal. $C_9H_{14}O_4N_2$ (214.22) Calc'd C, 50.46; H, 6.59; N, 13.08
Found : C, 50.37; H, 6.44; N, 12.94

An infrared spectrum of a liquid film of the redistilled product was recorded and showed $\lambda_{max.}$ at 5.66, 5.90, and 6.48 μ, among others. A nuclear magnetic resonance spectrum of the material was recorded in trifluoroacetic acid (TMS) and showed peaks at 5.56 τ (triplet, J=8 cps.), 6.36 τ (triplet, J=7 cps.), 7.04 τ (singlet), and 8.16 τ (poorly resolved multiplet).

Hydrogenation of 1-Succinimido-5-nitropentane

A solution of 0.196 g. (0.000915 mole) of 1-succinimido-5-nitropentane in 10 ml. of 95% ethyl alcohol was hydrogenated at 17° and 740 mm. pressure using 0.10 g. of 10% palladium on carbon (Matheson Coleman and Bell material, used as received) as the catalyst. The progress of the reaction was followed by measuring at approximately five-minute intervals the volume of hydrogen which had been absorbed. After 85 min., 57.8 ml. (0.00236 mole) of hydrogen had been taken up by the sample. The reaction was allowed to proceed for an additional 85 min., but no more hydrogen was absorbed. A graph of the volume of hydrogen absorbed versus time was plotted and a straight line could be drawn through all the points corresponding to volumes of hydrogen from 0 to 50 ml. (from 0 to 31 min.). The final 7.8 ml. of hydrogen were absorbed more slowly. The reaction mixture was filtered with suction to remove the catalyst, and the solvent was removed from the filtrate on a rotating evaporator at reduced pressure. The residual oil gave negative color tests with Benedict's reagent, Fehling's solution, and Tollen's reagent. It gave a purple color when warmed on a steam bath for five minutes with

ninhydrin reagent. An infrared spectrum of a liquid film of the material was recorded and showed $\lambda_{max.}$ at 2.95 (broad), 5.65, and 5.90 μ, among others. There was no absorption around 6.48 μ.

Paper chromatograms of the oily product in BAW and in BH were run. The chromatograms were developed with ninhydrin reagent. In each system there was observed only one spot, R_F 0.54 in BAW and 0.62 in BH.

Similar hydrogenations of 1-succinimido-5-nitropentane were accomplished using as catalysts 5% platinum on carbon (J. T. Baker and Company material, used as received) and 5% palladium on barium sulfate (Engelhard Industries material, used as received). The results were very similar to those reported above. When the hydrogenation was attempted in the presence of a 0.50 molar quantity of oxalic acid dihydrate with 5% palladium on barium sulfate as catalyst, no hydrogen was absorbed by the sample.

1-Succinimido-5-hydroxylaminopentane

To a solution of 28.0 g. (0.403 mole) of hydroxylamine hydrochloride in 3000 ml. of methyl alcohol (freshly distilled from magnesium turnings) was added with mechanical stirring 16.1 g. (0.403 mole) of sodium hydroxide pellets. A stream of dry nitrogen was bubbled through the resulting solution for 30 min. To the solution was added 10.0 g. (0.0403 mole) of 1-succinimido-5-bromopentane. The reaction solution was boiled under reflux for 48 hr. while nitrogen was slowly passed through the solution. The solvent was removed from the solution on a rotating evaporator at reduced pressure. To the residue were added 700 ml. of 5% hydrochloric acid solution and 200 ml. of chloroform. The organic layer was drawn off and the aqueous layer extracted with four 100-ml.

portions of chloroform.

The combined chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure to yield 5.13 g. of a material whose infrared spectrum was identical to that of 1-succinimido-5-bromopropane.

The aqueous portion was cooled to 10° in an ice-water bath and made alkaline to pH 8 by the dropwise addition of 28% ammonium hydroxide solution. The alkaline solution was extracted with ten 70-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure to yield 3.69 g. of a yellow liquid.

A sample of 1.50 g. of the liquid was purified by chromatography through a column containing 20 g. of silicic acid. The material was eluted successively with 180 ml. of chloroform and 150 ml. of 98% chloroform-2% ethyl alcohol. Using an automatic fraction collector, 2-ml. fractions were collected. The solvent was removed from the fractions on a rotating evaporator at reduced pressure. From one 25-ml. pooled fraction when the eluting solvent was 98% chloroform-2% ethyl alcohol there was obtained 0.284 g. of a clear gum. An infrared spectrum of a liquid film of the material was recorded and showed $\lambda_{max.}$ at 2.83, 2.90 (shoulder), 5.63, and 5.89 μ, among others. A nuclear magnetic resonance spectrum of the gum in carbon tetrachloride (TMS) was recorded and showed peaks at 2.32 τ (singlet), 6.62 τ (poorly resolved multiplet), 7.37 τ (singlet), and 8.58 τ (poorly resolved multiplet).

A paper chromatogram in BH was run on a sample of the gum. The chromatogram was developed with 2,3,5-triphenyl-2H-tetrazolium chloride reagent. The sample yielded two spots, R_F 0.34 and 0.68 [lit. (8) for naturally derived 1-succinimido-5-hydrox laminopentane in BH, 0.70]. Hydroxylamine hydrochloride showed an R_F value of 0.34 in BH. For analysis, a small portion of the gum was dried in vacuo.

Anal. $C_9H_{16}N_2O_3$ (200.24) Calc'd: C, 53.91; H, 8.05; N, 13.99
Found : C, 54.54; H, 7.38; N, 10.79

A solution of 0.024 g. of the above 1-succinimido-5-hydroxylaminopentane in 5 ml. of ethyl alcohol was hydrogenated at room temperature and atmospheric pressure using 0.07 g. of 10% palladium on carbon (Matheson Coleman and Bell material, used as received) as the catalyst. The hydrogenation was allowed to proceed for three hours. The reaction mixture was filtered with suction and the solvent removed from the filtrate on a rotating evaporator at reduced pressure. The residual yellow oil was dissolved in 1 ml. of 95% ethyl alcohol for paper chromatography in BAW and in BH. The chromatogram was developed with ninhydrin reagent. In each system there was observed only one spot, R_F 0.55 in BAW and 0.62 in BH.

The above preparation and chromatographic purification was repeated on a larger scale to obtain more 1-succinimido-5-hydroxylaminopentane. To a solution of 0.650 g. (0.00325 mole) of this material in 3 ml. of redistilled ethyl acetate was added dropwise a saturated solution of 0.146 g. (0.00163 mole) of anhydrous oxalic acid (26) in redistilled ethyl acetate. A yellow oil separated that would not dissolve when the reaction mixture was heated to boiling. After standing in a

refrigerator overnight, the oil had solidified. The cold reaction mixture was filtered with suction to yield 0.525 g., 66%, of a white solid, m.p. 109-113°. An aqueous solution of a sample of the solid gave a white precipitate on the addition of an aqueous calcium chloride solution. An infrared spectrum of a Nujol mull of the product was recorded and showed $\lambda_{max.}$ at 3.0 (broad), 5.63, and 5.89 μ, among others. A paper chromatogram in BH of a sample of the material was run. The chromatogram was developed with 2,3,5-triphenyl-2H-tetrazolium chloride reagent. The sample showed only one spot, R_F 0.76. A saturated solution of a portion of the product in boiling ethyl alcohol was prepared; when it was cooled in a refrigerator overnight, an amorphous solid precipitated. This process was twice repeated and the white powder, m.p. 110-112°, sent for analysis.

Anal.	$C_{20}H_{34}N_4O_{10}$	Calc'd:	C, 49.97; H, 6.99; N, 11.42
	(490.50)	Found :	C, 53.24; H, 7.15; N, 9.12

In an effort to determine the reliability of the hydroxylamino nitrogen analysis, an analytical sample of N-phenylhydroxylamine (24) was prepared by recrystallization three times from benzene to yield white crystals, m.p. 81-82° [lit. (25) 80-81°].

Anal.	C_6H_7NO	Calc'd:	C, 66.03; H, 6.47; N, 12.84
	(109.12)	Found :	C, 66.04; H, 6.33; N, 11.00

The Attempted Reaction of 1-Succinimido-5-hydroxylaminopentane with Sodium Methoxide in Methyl Alcohol

To ca. 2 ml. of methyl alcohol (freshly distilled from magnesium turnings) was added 0.026 g. (0.0011 g. atoms) of freshly cut sodium. When the evolution of gas had ceased, the solution was transferred to a 3-ml. volumetric flask and diluted to the mark with methyl alcohol

(freshly distilled from magnesium turnings). A 0.50-ml. (0.00019 mole of sodium methoxide) aliquot of the solution was added to a solution of 0.100 g. (0.000500 mole) of 1-succinimido-5-hydroxylaminopentane in 4.5 ml. of methyl alcohol (freshly distilled from magnesium turnings). For paper chromatography, 0.5-ml. samples of the reaction solution were withdrawn after 0, 1, 3-1/2, 7-1/2, and 24 hrs. The samples were worked up immediately by adding three drops of glacial acetic acid and evaporating the solution to dryness by means of a stream of dry nitrogen. The white solid residues were taken up in ca. 0.2 ml. of methyl alcohol and paper chromatograms run in BAW. The chromatograms were developed with ninhydrin reagent. The developed chromatograms of all of the samples showed only one spot, R_F 0.74.

Reduction of Nocardamine

A sample of authentic nocardamine was obtained from Dr. J. Renz of the Sandoz Laboratories, Basel, Switzerland. The material melted at 174-177° [lit. (1) 184°]. An infrared spectrum of a potassium bromide pellet of the compound was recorded and showed $\lambda_{max.}$ at 2.95, 6.17, and 6.46 μ, among others. A nuclear magnetic resonance spectrum of the compound in trifluoroacetic acid (TMS) was recorded and showed peaks at 1.62 τ (broad singlet), 5.92-7.26 τ (complex, poorly resolved multiplet), and 8.33 τ (poorly resolved multiplet).

A solution of 0.206 g. (0.000343 mole, assumed molecular weight, 600.70) of the above nocardamine in 100 ml. of hot ethyl alcohol was added to a mixture of 0.2 g. of Raney nickel (Raney Catalyst Company No. 28 Raney Active Nickel in Water) and 25 ml. of ethyl alcohol. The mixture was hydrogenated at 746 mm. pressure and 16°. After 50 min., the

apparent uptake of hydrogen by the mixture was 34.6 ml. (0.00143 mole, 4.20 moles/mole). [A blank determination using 100 ml. of hot ethyl alcohol was run. After 50 minutes, the apparent uptake of hydrogen was 26 ml.]. The hydrogenation was allowed to proceed for an additional 15 min., but no more hydrogen was absorbed by the solution. The reaction mixture was heated to boiling and the hot mixture filtered with suction. The residue was washed with three 75-ml. portions of hot ethyl alcohol. The solvent was removed from the combined filtrate and washings on a rotating evaporator at reduced pressure to yield 0.133 g., 70%, of a white crystalline solid, m.p. 267-270°. A solution of ca. 1 mg. of the material in ca. 1 ml. of ethyl alcohol gave no color when a solution of ferric chloride in ethyl alcohol was added. A nuclear magnetic resonance spectrum of the compound in trifluoroacetic acid (TMS) was recorded and showed peaks at 1.82 τ (broad singlet), 6.50 τ (poorly resolved multiplet), 7.04 τ (singlet), and 8.33 τ (poorly resolved multiplet). The spectrum is shown in Figure 2. For analysis, a portion of the product was recrystallized three times from redistilled n-butyl alcohol to yield white crystals, m.p. 279-281°.

Anal.	$C_{27}H_{48}N_6O_6$	Calc'd:	C, 58.67; H, 8.75; N, 15.21
	(552.70)	Found :	C, 59.03; H, 8.76; N, 14.90

An infrared spectrum of a potassium bromide pellet of the recrystallized product was recorded and showed $\lambda_{max.}$ at 3.07, 6.10, and 6.47 μ, among others. The spectrum is shown in Figure 1.

An attempt to measure the molecular weight of the compound using a Vapor Pressure Osmometer was unsuccessful. The material was insoluble in the usual organic solvents which may be used with this instrument.

The solubility of the recrystallized compound was less than 0.0057 g. in 7.0732 g. of water at room temperature. The material was soluble in trifluoroacetic acid.

1,6-Diaza-2,5-dioxocycloundecane

1,6-Diaza-2,5-dioxocycloundecane* was prepared by the reaction of succinyl chloride with 1,5-pentanediamine.

Anal. $C_9H_{16}N_2O_2$ (184.24) Calc'd: C, 58.66; H, 8.74; N, 15.21
Found : C, 58.87; H, 8.72; N, 15.10

When a sample of the compound was heated on the Kofler hot stage, it sublimed at ca. 160°; the melting point of the sublimate was not reproducible. When the material was heated in a sealed capillary, it melted at 218-221° (dec.). An infrared spectrum of a potassium bromide pellet of the compound was recorded and showed $\lambda_{max.}$ at 3.05, 6.10, and 6.47 μ, among others. The spectrum is shown in Figure 3. A nuclear magnetic resonance spectrum of the compound in trifluoroacetic acid (TMS) was recorded and showed peaks at 1.77 τ (broad singlet), 6.44 τ (poorly resolved multiplet), 7.00 τ (singlet), and 8.34 τ (poorly resolved multiplet). The spectrum is shown in Figure 4.

The molecular weight of the analytically pure compound was measured using a Vapor Pressure Osmometer. The observed molecular weights using solutions of 0.0100 g. of the compound in 5.1544 g. of water (ΔR = 0.72 ± 0.04), 0.0165 g. of compound in 5.0132 g. of water (ΔR = 1.16 ± 0.03), and 0.0223 g. of compound in 5.0198 g. of water (ΔR = 1.72 ± 0.10) were 179 ± 11, 189 ± 5, and 173 ± 11, respectively (calc'd for $C_9H_{16}N_2O_2$, 184).

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* The author would like to thank Daniel B. Dixon for the preparation of this compound.

Attempted Synthesis of 1,7,12,18,23,29-Hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane

4,10-Dioxo-5,9-diazatridecanedioic Acid

A solution of 67.50 g. (0.6750 mole) of succinic anhydride (Matheson Coleman and Bell material, m.p. 119-120°) in 3000 ml. of benzene (redistilled, b.p. 80°, and dried over sodium) was heated to boiling under reflux with mechanical stirring. To the boiling solution was added dropwise with stirring over a 1-1/2 hr. period 20.00 g. (0.2700 mole) of redistilled 1,3-propanediamine (b.p. 137-138°) in 250 ml. of benzene (redistilled, b.p. 80°, and dried over sodium). The reaction mixture was boiled under reflux with stirring for 14 hrs. and filtered while hot through a steam-jacketed Buchner funnel to yield 79.00 g., 106%, of white solid product, m.p. 156-159°. This material was crystallized from 375 ml. of hot water to yield 22.60 g., 31%, of white crystals, m.p. 159-161°, neutralization equivalent 141 (calc'd. for a diacid $C_{11}H_{18}N_2O_6$, 137). An infrared spectrum of a Nujol mull of the product was recorded and showed $\lambda_{max.}$ at 3.00, 3.75, 5.94, 6.14, and 6.55 μ, among others. A nuclear magnetic resonance spectrum of the compound in deuterium oxide (DSS) was recorded and showed peaks at 5.25 τ (singlet), 6.77 τ (triplet, J=7 cps.), 7.40 τ (triplet, J=4 cps.), and 8.30 τ (quintet, J=7 cps.). For analysis, a small portion of the product was recrystallized three times from distilled water to yield white crystals, m.p. 161-162°.

Anal. $C_{11}H_{18}N_2O_6$ (274.27) Calc'd: C, 48.17; H, 6.62; N, 10.22
Found : C, 48.15; H, 7.30; N, 10.09

4,12-Dioxo-5,11-diazapentadecanedioic Acid

A solution of 61.00 g. (0.6100 mole) of succinic anhydride

(Matheson Coleman and Bell material, m.p. 119-120°) in 2000 ml. of benzene (freshly distilled, b.p. 80°, and dried over sodium) was heated to boiling under reflux with mechanical stirring. To the boiling solution was added dropwise with stirring over a 1-1/2 hr. period 25.00 g. (0.2440 mole) of redistilled 1,5-pentanediamine (b.p. 177-179°) in 150 ml. of benzene (redistilled, b.p. 80°, and dried over sodium). The reaction mixture was boiled under reflux with stirring for 14 hrs. and filtered while hot through a steam-jacketed Buchner funnel to yield 71.50 g., 97%, of white solid product, m.p. 163-165°. This material was crystallized from 500 ml. of hot water to yield 57.40 g., 78%, of white crystals, m.p. 170-171°, neutralization equivalent 154 (calc'd. for a diacid $C_{13}H_{22}N_2O_6$, 151). An infrared spectrum of a Nujol mull of the product was recorded and showed $\lambda_{max.}$ at 3.03, 3.75, 5.93, 6.13, and 6.55 μ, among others. A nuclear magnetic resonance spectrum of the compound in deuterium oxide (DSS) was recorded and showed peaks at 5.29 τ (singlet), 6.81 τ (triplet, J=7 cps.), 7.40 τ (triplet, J=3 cps.), and 8.57 τ (poorly resolved multiplet). For analysis, a small portion of the product was recrystallized three times from distilled water to yield white crystals, m.p. 170-171°.

Anal.	$C_{13}H_{22}N_2O_6$	Calc'd:	C, 51.64; H, 7.34; N, 9.27
	(302.32)	Found :	C, 51.42; H, 7.50; N, 9.30

The Attempted Preparation of 1,12-Diamino-4,9-diaza-5,8-dioxdodecane

(a) By the Reaction of 1,3-Propanediamine with Succinyl Chloride. To a mechanically stirred solution of 38.20 g. (0.5160 mole) of redistilled 1,3-propanediamine (b.p. 137-138°) in 300 ml. of benzene (redistilled, b.p. 80°, and dried over sodium) was added dropwise over a 1-1/2 hr.

period at room temperature a solution of 10.00 g. (0.06450 mole) of succinyl chloride (Eastman Kodak White Label material, used as received) in 100 ml. of benzene (redistilled, b.p. 80°, and dried over sodium). The reaction mixture was stirred at room temperature for four hours and filtered with suction to obtain 26.20 g. of a white solid. Paper chromatograms in BAW and in BH of samples of the solid and of 1,3-propanediamine were run. The chromatograms were developed with ninhydrin reagent. Each of the samples gave only one (identical)spot, R_F 0.58 in BAW and 0.14 in BH.

(b) By the Reaction of 1,3-Propanediamine with Diethyl Succinate. To 12.60 g. (0.1720 mole) of redistilled 1,3-propanediamine (b.p. 137-138°) was added 3.00 g. (0.0172 mole) of diethyl succinate (Eastman Kodak White Label material, used as received). The resulting solution was allowed to stand at room temperature for 22 hrs. The reaction mixture was filtered with suction to remove 0.940 g. of a white gelatinous solid. An infrared spectrum of a film of the solid was recorded and showed no absorption from 5.50 to 6.10 μ. An infrared spectrum of a liquid film of the filtrate was recorded and showed $\lambda_{max.}$ at 6.03 μ, among others; there was no absorption from 5.50 to 6.02 μ. Paper chromatograms in BAW and in BH of samples of the solid, the filtrate, and 1,3-propanediamine were run. The chromatograms were developed with ninhydrin reagent. Each of the samples gave only one (identical) spot, R_F 0.66 in BAW and 0.16 in BH.

(c) By the Reaction of 1,3-Propanediamine with Diethyl Succinate in Benzene. To a solution of 3.00 g. (0.0172 mole) of diethyl succinate (Eastman Kodak White Label material, used as received) in 100 ml. of

benzene (redistilled, b.p. 80°, and dried over sodium) was added 12.60 g. (0.172 mole) of redistilled 1,3-propanediamine (b.p. 137-138°). The reaction solution was boiled under reflux on a steam bath. After 4 hrs., 22 hrs., 48 hrs., and five days, 20-ml. aliquots of the reaction solution were withdrawn, the benzene removed from the samples on a rotating evaporator at reduced pressure, and infrared spectra of liquid films of the residues recorded. The spectra of the samples which had been withdrawn after 4, 22, and 48 hrs. showed $\lambda_{max.}$ at 5.76 μ. The spectrum of the sample withdrawn after five days showed $\lambda_{max.}$ at 6.05 and 6.34 μ; this sample showed no absorption from 5.50 to 6.05 μ. Paper chromatograms in BAW and i BH of samples of 1,3-propanediamine and of the residue corresponding to a reaction time of five days were run. The chromatograms were developed with ninhydrin reagent. Each of the samples gave only one (identical) spot, R_F 0.62 in BAW and 0.14 in BH.

6,11-Diaza-7,10-dioxohexadecane

A solution of 5.60 g. (0.0645 mole) of 1-aminopentane (Eastman Kodak White Label material, used as received) in 50 ml. of benzene (redistilled, b.p. 80°, and dried over sodium) was cooled with mechanical stirring to 10° in an ice-water bath. To the solution was added dropwise with stirring over a 30-min. period a solution of 2.00 g. (0.0129 mole) of succinyl chloride (Eastman Kodak White Label, used as received) in 10 ml. of benzene (redistilled, b.p. 80°, and dried over sodium). The reaction mixture was stirred in the cold for 30 min., heated to boiling on a steam bath to effect solution, and allowed to cool to room temperature. The resulting mixture was filtered with suction and the white crystalline residue washed with 25 ml. of cold water. The product was dried

in vacuo over calcium chloride to yield 2.49 g., 75%, of white crystals. When a sample of the material was heated on the Kofler hot stage, it sublimed at ca. 140° and the sublimate melted sharply at 181°. An infrared spectrum of a chloroform solution of the compound was recorded and showed $\lambda_{max.}$ at 2.80, 2.94, 6.00, and 6.55 μ, among others. A nuclear magnetic resonance spectrum of the material in deuterochloroform (TMS) was recorded and showed peaks at 3.0 τ (broad singlet), 6.78 τ (poorly resolved multiplet), 7.43 τ (singlet), 8.63 τ (poorly resolved multiplet), and 9.11 τ (triplet, J=5 cps.). For analysis, a portion of the product was sublimed in vacuo three times at ca. 140°/0.5 mm. to yield white crystals, m.p. 181° after sublimation at ca. 140°.

Anal.	$C_{14}H_{28}O_2N_2$	Calc'd:	C, 65.59; H, 11.01; N, 10.93
	(256.39)	Found :	C, 64.97; H, 10.73; N, 10.85

Purification and Analysis of Carbobenzoxyl Chloride

The carbobenzoxy chloride used in the subsequent reactions was analyzed by nuclear magnetic resonance spectroscopy.

A nuclear magnetic resonance spectrum of carbobenzoxy chloride (Columbia Organic Chemicals Company material, as received) in carbon tetrachloride (TMS) was recorded and showed peaks at 2.76 τ (complex multiplet), 4.78 τ (singlet, 3.5 integration units), 4.87 τ (singlet, 1.2 integration units), 5.48 τ (singlet, 4.2 integration units), and 7.67 τ (singlet, 1.1 integration units). A portion of this material was distilled in vacuo at 0.3-4 mm. and a bath temperature of 70°; approximately equal volumes of distillate and residue were obtained. A nuclear magnetic resonance spectrum of the distillate in carbon tetrachloride (TMS) was recorded and showed peaks at 2.76 τ (complex multiplet),

4.78 τ (singlet, 1.7 integration units), 5.49 τ (singlet, 7.2 integration units), and 7.67 τ (singlet, 2.1 integration units). A nuclear magnetic resonance spectrum of the residue in carbon tetrachloride (TMS) was recorded and showed peaks at 2.75 τ (complex multiplet), 4.77 τ (singlet, 7.3 integration units), 4.89 τ (singlet, 3.5 integration units), and 5.49 τ (singlet, 1.2 integration units).

A small portion of carbobenzoxy chloride (Columbia Organic Chemicals Company material, as received) was distilled in vacuo; fractions boiling at 40-58°/1 mm. (fraction 1), 58-62°/1-3 mm., 62-83°/3 mm., and 83-85°/3 mm. (fraction 4) were collected. A nuclear magnetic resonance spectrum of fraction 1 in carbon tetrachloride (TMS) was recorded and showed peaks at 2.84 τ (complex multiplet), 4.83 τ (singlet, 1.5 integration units), and 5.54 τ (singlet, 7.9 integration units). A nuclear magnetic resonance spectrum of fraction 4 in carbon tetrachloride (TMS) was recorded and showed peaks at 2.67 τ (singlet) and 4.78 τ (singlet).

A nuclear magnetic resonance sprectrum of toluene [neat liquid (TMS)] showed peaks at 2.97 τ (poorly resolved multiplet) and 7.87 τ (singlet). A nuclear magnetic resonance spectrum of benzyl chloride in carbon tetrachloride (TMS) showed peaks at 2.74 τ (singlet) and 5 52 τ (singlet). A nuclear magnetic resonance spectrum of benzal chloride in carbon tetrachloride (TMS) showed peaks at 2.57 τ (complex multiplet) and 3.37 τ (singlet).

A nuclear magnetic resonance spectrum of carbobenzoxy chloride (Nutritional Biochemicals Corporation material, as received) in carbon tetrachloride (TMS) was recorded and showed peaks at 2.64 τ (complex multiplet), 4.75 τ (singlet, 17.4 integration units), and 5.48 τ (singlet,

4.1 integration units). A portion of this material was distilled in vacuo at 1 mm. and a bath temperature of 60°; ca. 80% of the material remained as residue. A nuclear magnetic resonance spectrum of the residue in carbon tetrachloride (TMS) was recorded and showed peaks at 2.63 τ (complex multiplet), 4.73 τ (singlet, 17.3 integration units), and 5.46 τ (singlet, 2.1 integration units).

Attempted Preparation of 1-Carbobenzoxyamino-3-aminopropane by the Reaction of 1,3-Propanediamine with Carbobenzoxy Chloride

(a) Under Schotten-Baumann Conditions. A solution of 3.68 g. (0.0498 mole) of redistilled 1,3-propanediamine (b.p. 137-138°) in 20 ml. (0.05 mole) of 10% sodium hydroxide solution was cooled in an ice-water bath with magnetic stirring to 10°. To the cold solution was added dropwise with stirring over a 1-1/2 hr. period 8.50 g. (0.0409 mole) of 82% carbobenzoxy chloride. The reaction mixture was stirred at ca. 10° for 2-1/2 hrs. and acidified to pH 1 by the dropwise addition of 4 N hydrochloric acid solution. The acidic mixture was extracted with three 60-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure to yield 7.14 g., 102%, of a white solid, m.p. 114-116°. An infrared spectrum of a chloroform solution of the compound was recorded and showed $\lambda_{max.}$ at 2.83, 5.85, and 6.63 μ, among others. A nuclear magnetic resonance spectrum of the material in deuterochloroform (TMS) was recorded and showed peaks at 2.65 τ (singlet), 4.62 τ (broad, poorly resolved multiplet), 4.90 τ (singlet), 6.81 τ (quartet, J= 6 cps.), and 8.42 τ (quintet, J=7 cps.). For analysis, a portion of the product was recrystallized three times from ethyl alcohol

to yield white crystals, m.p. 118.0-118.5°.

Anal. $C_{19}H_{22}N_2O_4$ (342.39) Calc'd: C, 66.62; H, 6.48; N, 8.18
Found : C, 67.30; H, 6.41; N, 7.94

(b) In Ether. A solution of 9.22 g. (0.125 mole) of redistilled 1,3-propanediamine (b.p. 137-138°) and 22.50 g. (0.2500 mole) of redistilled triethylamine (b.p. 88-89°) in 100 ml. of anhydrous ether (Merck Reagent material, dried over sodium) was cooled in an ice-water bath with mechanical stirring to 10°. To the cold solution was added dropwise with stirring over a 1-1/2-hr. period a solution of 4.25 g. (0.0204 mole) of 82% carbobenzoxy chloride in 25 ml. of anhydrous ether (Merck Reagent material, dried over sodium). The reaction mixture was stirred at ca. 10° for 1-1/2 hr. and the ether removed from the mixture on a rotating evaporator at reduced pressure. To the residue was added 100 ml. of 4 N hydrochloric acid solution. The acidic mixture was extracted with three 75-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure to yield 1.61 g., 46%, of 1,3-bis-carbobenzoxyaminopropane, m.p. 113-115°. The aqueous solution was cooled in an ice-water bath to 10° and made alkaline to pH 10 by the dropwise addition of 4 N sodium hydroxide solution. The alkaline solution was extracted with three 100-ml. portions of ether. The ether extracts were dried over magnesium sulfate and filtered. The ether was removed from the filtrate on a rotating evaporator at reduced pressure to yield 1.05 g. of a yellow liquid. An infrared spectrum of a liquid film of the material was recorded and showed $\lambda_{max.}$ at 2.96, 5.85, and 6.51 μ, among others. A paper chromatogram in BAW of samples of the

above liquid and of 1,3-propanediamine were run. The chromatograms were developed with ninhydrin reagent. The sample of 1,3-propanediamine showed only one spot, R_F 0.74. The sample of the liquid reaction product showed two spots, R_F 0.78 and 0.84.

Attempted Preparation of 1-Carbobenzoxyamino-5-aminopentane

A solution of 9.25 g. (0.0906 mole) of redistilled 1,5-pentanediamine (b.p. 177-179°) and 30.50 g. (0.3020 mole) of redistilled triethylamine (b.p. 88-89°) in 150 ml. of chloroform was cooled in an ice-water bath with mechanical stirring to 10°. To the cold solution was added dropwise with stirring over a 1-1/2-hr. period a solution of 5.80 g. (0.0302 mole) of 90% carbobenzoxy chloride in 30 ml. of chloroform. The reaction mixture was stirred at ca. 10° for 1-1/2 hr. The chloroform was removed from the mixture on a rotating evaporator at reduced pressure. To the yellow liquid residue was added 100 ml. of water. The resulting mixture was cooled to 10° in an ice-water bath and acidified to pH 1 by the dropwise addition of 4 N hydrochloric acid solution. The acidic mixture was extracted with three 100-ml. portions of chloroform.

The aqueous portion was cooled in an ice-water bath to 10° and made alkaline to pH 11 by the dropwise addition of 4 N sodium hydroxide solution. The alkaline solution was extracted with three 100-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure. The residue was heated at 60°/1mm. for one hour in an effort to remove any remaining 1,5-pentanediamine. The residual yellow liquid weighed 3.78 g. An infrared spectrum of a liquid film of the material was recorded and showed

$\lambda_{max.}$ at 3.00, 5.85, and 6.52 μ, among others. A paper chromatogram in BH of samples of the liquid and of 1,5-pentanediamine was run. The chromatogram was developed with ninhydrin reagent. The 1,5-pentanediamine sample showed only one spot, R_F 0.17. The sample of the liquid product showed two spots, R_F 0.56 and 0.96.

Vacuum distillation of a portion of the above liquid product was attempted. Distillation at 138°/3 mm. was accompanied by the evolution of gas. An infrared spectrum of a liquid film of the distillate was recorded; it showed no absorption from 5.50 to 6.00 μ.

A 1.391-g. portion of the above liquid reaction product was dissolved in 15 ml. of anhydrous ether (Merck Reagent material, dried over sodium) and the solution saturated with hydrogen chloride gas. The resulting mixture was filtered by gravity and the solid residue washed with four 25-ml. portions of ether. The residue weighed 1.321 g. This material was crystallized from hot n-butyl alcohol to yield white crystals, m.p. 225-240°. A paper chromatogram in BH of a sample of the crystalline product was run. The chromatogram was developed with ninhydrin reagent. The sample showed only one spot, R_F 0.58. An infrared spectrum of a Nujol mull of the material was recorded; it showed no absorption from 5.50 to 6.00 μ. For analysis, a small portion of the product was recrystallized three times from n-butyl alcohol to give white crystals, m.p. 249-252°.

Anal. $C_{13}H_{21}ClN_2O_2$ (272.77) Calc'd: C, 57.24; H, 7.76; Cl, 13.00; N, 10.27

$C_{12}H_{22}Cl_2N_2$ (266.32) Calc'd: C, 54.34; H, 8.36; Cl, 26.74; N, 10.56
Found : C, 55.28; H, 8.57; Cl, 25.67; N, 10.38

1-Amino-5-nitropentane Hydrochloride

1-Phthalimido-5-bromopentane was prepared according to Drake and Garman (27) from 92.60 g. (0.5000 mole) of potassium phthalimide (28) and 229.0 g. (1.000 mole) of 1,5-dibromopentane. The product was recrystallized from ethyl alcohol to yield 104.4 g., 71%, of white crystals, m.p. 59-60° [lit. (29) 61°].

1-Phthalimido-5-nitropentane was prepared by the method of Bickel, et al. (30) from 86.30 g. (0.2920 mole) of 1-phthalimido-5-bromopentane and 58.50 g. (0.380 mole) of silver nitrite which had been purified according to Vogel (31). The yield of crude liquid product was 78.00 g., 102%.

1-Amino-5-nitropentane hydrochloride (30) was prepared from 76.60 g. (0.2930 mole) of crude 1-phthalimido-5-nitropentane and 15.10 g. (0.3010 mole) of hydrazine hydrate. After conversion to the hydrochloride salt, the yield of crude product was 41.60 g., 84%. This material was twice recrystallized from n-propyl alcohol to yield pale yellow crystals, m.p. 108-114 [lit. (16) 113-115°].

Attempted Preparation of 1,16-Dinitro-6,11-diaza-7,10-dioxohexadecane by the Reaction of 1-Amino-5-nitropentane with Succinyl Chloride

(a) In N,N-Dimethylformamide. An ion-exchange column containing 60 ml. of Amberlite IR 45 anion exchange resin in the hydroxide phase was prepared in a 100-ml. buret; 50% aqueous ethyl alcohol was used as the solvent. A solution of 1.010 g. (0.006020 mole) of 1-amino-5-nitropentane hydrochloride in 10 ml. of 50% aqueous ethyl alcohol was applied to the column. The sample was eluted with 180 ml. of 50% aqueous ethyl alcohol, and the solvent removed from the eluent on a rotating evaporator

at reduced pressure to yield 0.761 g., 96%, of a yellow oil. An infrared spectrum of a liquid film of the oil was recorded and showed $\lambda_{max.}$ at 2.86, 3.05, and 6.44 μ, among others.

The oil was dissolved in 10 ml. of redistilled N,N-dimethylformamide (b.p. 150-152°) and the solution cooled to 10° in an ice-water bath. To the solution was added dropwise over a 30-min. period a solution of 0.186 g. (0.00120 mole) of succinyl chloride (Eastman Kodak White Label material, used as received) in 1 ml. of redistilled N,N-dimethylformamide. The solution was allowed to stand at ca. 10° for 30 min., heated under reflux on a steam bath for 30 min., and allowed to cool to room temperature. The N,N-dimethylformamide was removed from the solution by distillation in vacuo. To the residual brown tar was added 15 ml. of 5% hydrochloric acid solution. The resulting mixture was extracted with three 10-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure to yield 0.130 g. of a dark brown oil. An infrared spectrum of a chloroform solution of the oil was recorded and showed $\lambda_{max.}$ at 2.94, 5.76, 6.04, and 6.48 μ, among others.

(b) In Benzene. A sample of 0.742 g. (0.00562 mole) of oily 1-amino-5-nitropentane was prepared from 1.010 g. (0.006020 mole) of 1-amino-5-nitropentane hydrochloride using the ion-exchange treatment described previously. To the oil was added 20 ml. of benzene (redistilled, b.p. 80°, and dried over sodium). The mixture was cooled with magnetic stirring in a tap water bath. To the mixture was added with stirring over a 1-1/2-hr. period a solution of 0.174 g. (0.00112 mole) of succinyl chloride (Eastman Kodak White Label material, used as received) in 10 ml. of benzene (redistilled,

b.p. 80°, and dried over sodium). The reaction mixture was stirred at ca. 15° for two hours, boiled under reflux on a steam bath for 30 min., and allowed to cool to room temperature. The benzene solution was removed from the insoluble gum by decantation.

To the gum was added 10 ml. of 5% hydrochloric acid solution. The resulting solution was extracted with three 10-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure to yield 0.028 g. of a brown gum. An infrared spectrum of a chloroform solution of the gum was recorded and showed $\lambda_{max.}$ at 5.86, 5.98, and 6.46 μ, among others.

The solvent was removed from the benzene solution on a rotating evaporator at reduced pressure to yield 0.132 g. of a brown gum. An infrared spectrum of a chloroform solution of the gum was recorded and showed $\lambda_{max.}$ at 5.58, 5.80, and 6.43 μ, among others.

4-Oxo-5-aza-10-carbobenzoxyaminodecanoic Acid

In a three-liter flask fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel which was heated to 80° with electrical heating tape, a solution of 18.00 g. (0.1800 mole) of a succinic anhydride (Matheson Coleman and Bell material, m.p. 119-120°) in 1500 ml. of boiling benzene (redistilled, b.p. 80°, and dried over sodium) was added dropwise over a two-hour period to a boiling, stirred solution of 73.58 g. (0.7200 mole) of redistilled 1,5-pentanediamine (b.p. 177-179°) in 500 ml. of boiling benzene (redistilled, b.p. 80°, and dried over sodium). The reaction mixture was boiled under reflux with stirring for three hours, cooled to room temperature, and the benzene solution

removed by decantation from the white gummy product. The gum was dissolved in 200 ml. of water, transferred to a one-liter flask, and cooled to 10° in an ice-water bath. To the solution were added concurrently over a one-hour period with mechanical stirring 210 ml. (0.840 mole) of 4 N sodium hydroxide solution and 118 g. (0.600 mole) of 87% carbobenzoxy chloride. The reaction mixture was stirred in the cold for one hour and filtered with suction. The filtrate was extracted with three 100-ml. portions of ether. The aqueous portion was cooled to 10° in an ice-water bath and acidified to pH 1 by the dropwise addition of 6 N hydrochloric acid solution. The cold acidic solution was filtered with suction; there was obtained 8.78 g. of a white solid, m.p. 128-131°. The filtrate was extracted with three 100-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure to yield an additional 1.19 g. of the white solid product. The total yield was 9.97 g., 26%. The product was crystallized from hot water to yield white crystals, m.p. 129-131°, neutralization equivalent 338 (calc'd. for a monobasic acid $C_{17}H_{24}N_2O_5$, 336). An infrared spectrum of a chloroform solution of the compound was recorded and showed $\lambda_{max.}$ at 2.81, 2.92, 3.73, 5.82, 6.00, and 6.57 μ, among others. For analysis, a small portion of the material was recrystallized three times from distilled water to yield white crystals, m.p. 129-131°.

Anal.	$C_{17}H_{24}N_2O_5$	Calc'd:	C, 60.70; H, 7.19; N, 8.33
	(336.48)	Found :	C, 60.78; H, 7.20; N, 8.46

Attempted Preparation of 1-Carbobenzoxyamino-6,11-diaza-7,10-dioxo-16-aminohexadecane

A solution of 1.000 g. (0.002980 mole) of 4-oxo-5-aza-10-carbobenzoxyaminodecanoic acid, 0.914 g. (0.00894 mole) of redistilled 1,5-pentanediamine (b.p. 179-180°), and 0.614 g. (0.00298 mole) of dicyclohexylcarbodiimide (Eastman Kodak White Label material, used as received) in 200 ml. of redistilled N,N-dimethylformamide (b.p. 150-152°) was magnetically stirred at room temperature for 17 hr. The N,N-dimethylformamide was removed from the reaction on a rotating evaporator at 2 mm. and a bath temperature of 80°. The yellow liquid residue weighed 3.105 g. To the residue was added 40 ml. of 5% hydrochloric acid solution. The resulting mixture was filtered with suction and the filtrate extracted with three 25-ml. portions of chloroform.

The acidic aqueous solution was made alkaline to pH 8 by the dropwise addition of 5% sodium bicarbonate solution. The alkaline solution was extracted with ten 40-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure. The residue was heated at 80°/2 mm. for two hours in an effort to remove any remaining 1,5-pentanediamine. The residual brown gum weighed 0.115 g. (9%, based on a molecular weight of 420). An infrared spectrum of a chloroform solution of the gum was recorded and showed $\lambda_{max.}$ at 2.79, 3.00, 5.83, 6.00, 6.20, and 6.6 (broad) μ, among others. Paper chromatograms in BAW and BH were run on samples of the gum and of 1,5-pentanediamine. The chromatograms were developed with ninhydrin reagent. The sample of 1,5-pentanediamine showed only one spot, R_F 0.54 in BAW and 0.15 in BH. The sample of the gummy product showed only one spot, R_F 0.82 in

BAW and 0.84 in BH.

To the remainder of the above gum (0.000238 mole, based on a molecular weight of 420) was added 10 ml. of water and 1 ml. of 4 N sodium hydroxide solution. The cloudy solution was cooled in an ice-water bath. To the solution was added 0.120 g. (0.000567 mole) of 81% carbobenzoxy chloride in 5 ml. of anhydrous ether (Merck Reagent material, dried over sodium). The reaction mixture was magnetically stirred for 1-1/2 hr. and extracted with five 10-ml. portions of chloroform. The chloroform extracts were dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure and the residual brown liquid washed with two 10-ml. portions of light petroleum ether. The petroleum ether was removed by decantation. The residual yellow gum weighed 0.040 g. (32%, based on a molecular weight of 554).

1-Carbobenzoxyamino-6,11-diaza-7,10-dioxo-16-nitrohexadecane

A sample of 0.288 g. (0.00170 mole) of 1-amino-5-nitropentane hydrochloride was converted into oily 1-amino-5-nitropentane by the ion-exchange treatment described previously. The oil was dissolved in 4 ml. of pyridine (Matheson Coleman and Bell Reagent material, used as received). The solution was added to a solution of 0.572 g. (0.00170 mole) of 4-oxo-5-aza-10-carbobenzoxyaminodecanoic acid and 0.350 g. (0.00170 mole) of redistilled dicyclohexylcarbodiimide (b.p. 126-127/3 mm.) in 8 ml. of pyridine (Matheson Coleman and Bell Reagent material, used as received). The reaction solution was magnetically stirred at room temperature for 19 hr. At this time, a white solid was present in the reaction mixture. A 0.2-ml. aliquot of the supernatant solution was withdrawn and

added to 0.4 ml. of chloroform. An infrared spectrum of the resulting solution was recorded and showed $\lambda_{max.}$ at 2.96, 5.82, 6.00, 6.30, and 6.42 μ, among others; there was no absorption from 4.00 to 5.00 μ.

The remaining reaction mixture was filtered with suction to remove 0.260 g., 68%, of crystalline N,N'-dicyclohexylurea. When this material was heated on the Kofler hot stage, it sublimed at ca. 150° and the sublimate melted sharply at 220°. The pyridine was removed from the filtrate on a rotating evaporator at reduced pressure. The residual brown gum was dissolved in 15 ml. of chloroform and the solution extracted successively with three 10-ml. portions of 5% hydrochloric acid solution, three 10-ml. portions of 5% sodium bicarbonate solution, and one 10-ml. portion of water. The chloroform solution was dried over magnesium sulfate and filtered. The chloroform was removed from the filtrate on a rotating evaporator at reduced pressure to yield 0.614 g., 80%, of a yellow solid, m.p. 120-124°. The product was crystallized from water to yield white crystals, m.p. 134-137°. An infrared spectrum of a chloroform solution of the compound was recorded and showed $\lambda_{max.}$ at 2.81, 2.93, 5.83, 6.02, 6.45, and 6.61 μ, among others. For analysis, a portion of the product was recrystallized three times from 50% aqueous ethyl alcohol to give white crystals, m.p. 137-138°.

Anal. $C_{22}H_{34}N_2O_6$ (450.54) Calc'd: C, 58.65; H, 7.61; N, 12.44
Found : C, 58.91; H, 7.61; N, 11.70

Attempted Preparation of 1,7,12,18,23,29-Hexaaza-8,11,19,22,30,33-hexaoxocyclotritriacontane

A solution of 1.74 g. (0.00386 mole) of 1-carbobenzoxyamino-6,11-diaza-7,10-dioxo-16-nitrohexadecane in 100 ml. of hot ethyl alcohol was

added to a mixture of 0.50 g. of 10% palladium on carbon (Matheson Coleman and Bell material, used as received) and 25 ml. of ethyl alcohol. The mixture was hydrogenated at 736 mm. pressure and 22°. The hydrogenation was allowed to proceed for 18 hr. The apparent uptake of hydrogen by the solution was 340 ml. (0.0136 mole). The reaction mixture was heated to boiling and the hot mixture filtered with suction. The residue was washed with three 50-ml. portions of hot ethyl alcohol. The solvent was removed from the combined filtrate and washings on a rotating evaporator at reduced pressure and the white solid residue dried in vacuo at room temperature and 1 mm. for 1-1/2 hr. The yield of white solid product, m.p. 120-128°, was 1.135 g., 102%. An infrared spectrum of a saturated chloroform solution of the material was recorded and showed $\lambda_{max.}$ at 2.80, 2.95, 6.02, and 6.56 μ, among others. A paper chromatogram in BH of a sample of the product was run. The chromatogram was developed with ninhydrin reagent; it showed only one spot, R_F 0.22.

The remainder of the above product was dissolved in 100 ml. of redistilled N,N-dimethylformamide (b.p. 150-152°). The solution was added to a solution of 1.166 g. (0.003860 mole) of 4,12-dioxo-5,11-diazapentadecanedioic acid in 200 ml. of redistilled N,N-dimethylformamide (b.p. 150-152°). A small quantity of white solid material separated from the solution; it did not dissolve when the mixture was magnetically stirred. To the mixture was added a solution of 1.590 g. (0.007720 mole) of redistilled dicyclohexylcarbodiimide (b.p. 126-127°/3 mm.) in 10 ml. of redistilled N,N-dimethylformamide (b.p. 150-152°). The reaction mixture was magnetically stirred at room temperature for 40 hr.

At this time, a 5-ml. aliquot of the supernatant reaction solution

was withdrawn. The N,N-dimethylformamide was removed from the solution *in vacuo*. To the gummy residue was added 1 ml. of chloroform; the gum solidified. The mixture was filtered by gravity. An infrared spectrum of the filtrate was recorded; it showed no absorption from 4.30 to 5.50 μ.

The reaction mixture was filtered with suction. The white solid residue (fraction 1) was dried *in vacuo* at 100° and 1 mm.; it weighed 0.778 g. The N,N-dimethylformamide was removed from the filtrate *in vacuo* on a rotating evaporator at 1 mm. and a bath temperature of 80°. The residual yellow solid (fraction 2) was dried *in vacuo* at 80° and 1 mm.; it weighed 2.386 g.

Fraction 2 was extracted continuously for 18 hr. with benzene (redistilled, b.p. 80°, and dried over sodium) in a Soxhlet extraction apparatus. The residue (fraction 3) was recovered. The solvent was removed from the benzene extract on a rotating evaporator at reduced pressure to yield 1.920 g. of a yellow solid (fraction 4).

To fraction 4 was added 50 ml. of water. The mixture was heated to boiling and filtered while hot through a steam-jacketed Buchner funnel. The residue (fraction 5) was recovered; when it was heated on the Kofler hot stage, it sublimed at *ca.* 160° and the sublimate melted at 200-205°. The water was removed from the filtrate on a rotating evaporator at reduced pressure. The residual yellow gum (fraction 6) was dried *in vacuo* at room temperature and 0.5 mm.; it weighed 0.169 g. Fraction 6 was placed in a refrigerator for 24 hr.; it did not solidify.

Fraction 1 was extracted continuously for 18 hr. with benzene (redistilled, b.p. 80°, and dried over sodium) in a Soxhlet extraction apparatus. The solvent was removed from the benzene extract on a rotating

evaporator at reduced pressure. There was no (0.000 g.) residue.

Paper chromatograms in BH and in 77% ethyl alcohol-23% water (EW) of samples of fractions 1, 3, and 6 and of the reduction product of authentic nocardamine (XXII) were run. The chromatograms were developed according to Rydon and Smith (32). The dried chromatograms were exposed to chlorine gas for 30 min. and placed in the hood for three hours. The chromatograms were then sprayed with an aqueous 1% soluble starch-1% potassium iodine solution; intense blue-black spots appeared against a faint blue background. The R_F values are shown in Table 2.

Table 2. R_F Values of the Materials Obtained from the Reaction of XXIII and XXIV with Dicyclohexylcarbodiimide.

	R_F in BH	R_F in EW
XXXII	0.85	0.76
Fraction 1	0.22	0.46
Fraction 3	1.00	0.86
Fraction 6	1.00	0.84

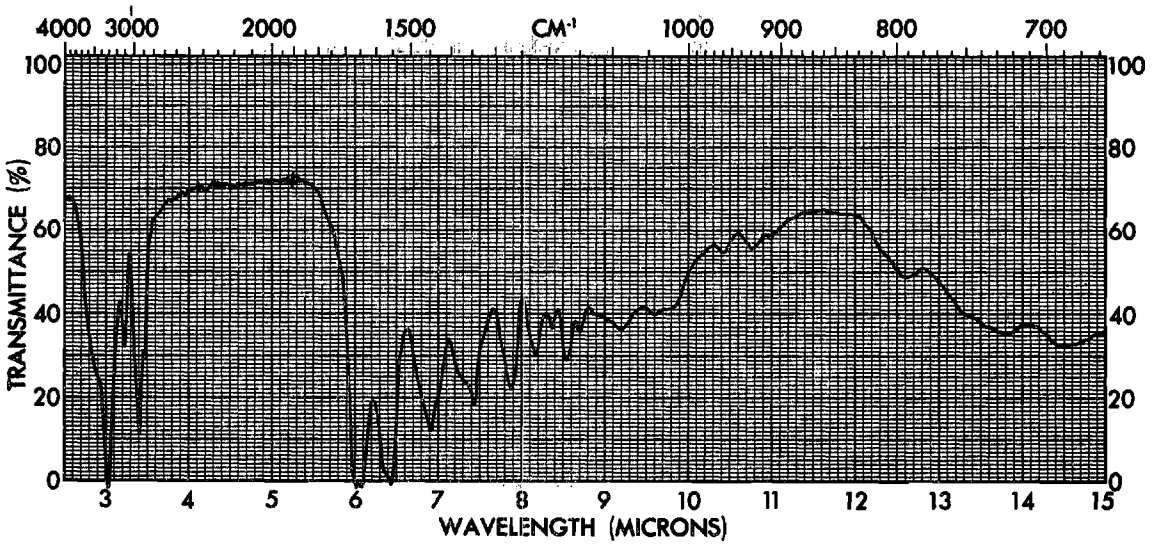

Figure 1. The Infrared Spectrum of the Reduction Product of Nocardamine.

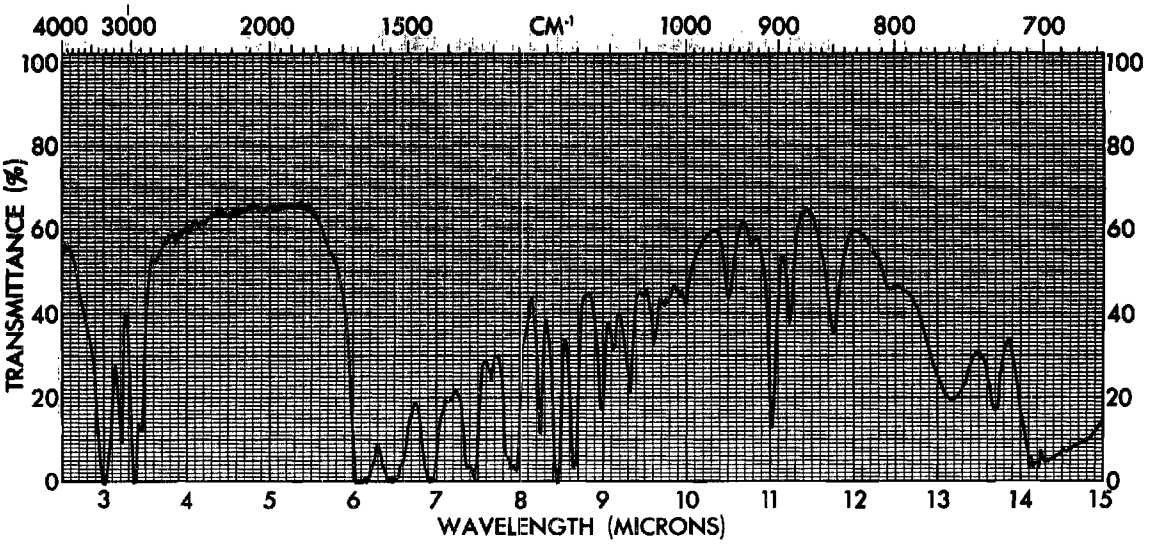

Figure 3. The Infrared Spectrum of 1,6-Diaza-2,5-dioxocycloundecane.

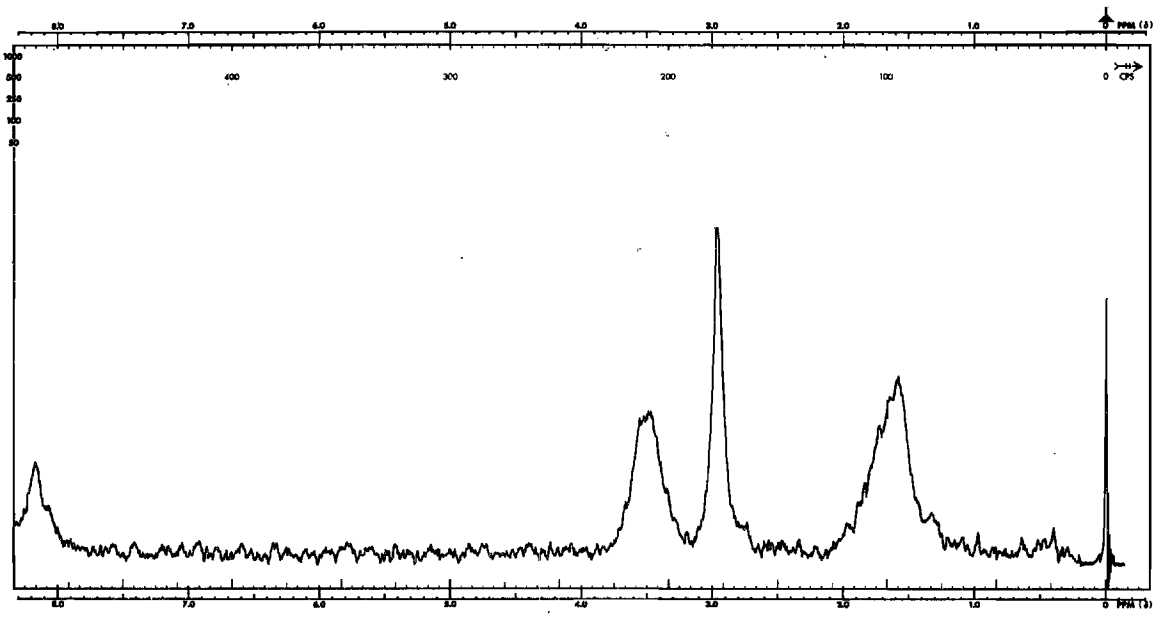

Figure 2. The Nuclear Magnetic Resonance Spectrum of the Reduction Product of Nocardamine.

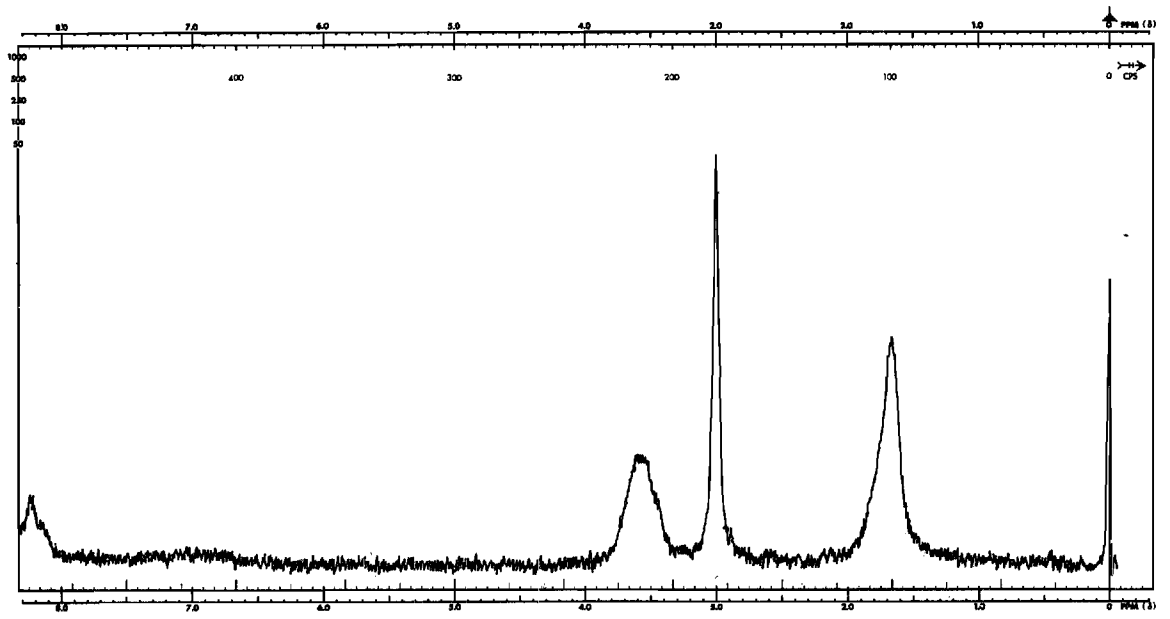

Figure 4. The Nuclear Magnetic Resonance Spectrum of 1,6-Diaza-2,5-dioxocycloundecane.

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VITA

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